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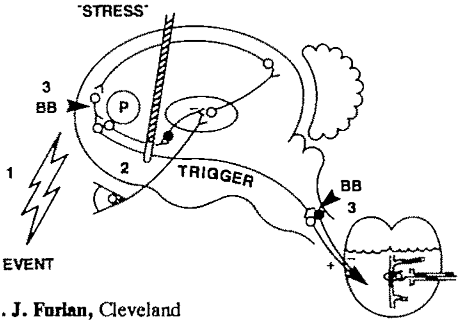

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The new glossy finish for the cover of *Brain* has been introduced to make it more durable and less liable to become soiled. This innovation provides the opportunity of reiterating the type of paper accepted by the journal. *Brain* publishes original papers on clinical neurology and neuropsychology and on basic neuroscience if relevant to the understanding of neurological disorders. Studies purely on normal material are not usually accepted. *Brain* does not publish preliminary reports of work in progress or brief single case reports, but papers based on single cases will be considered if they add significant new insights or lead to the development of new principles. Although brevity is encouraged, *Brain* is prepared to accept longer papers, including review articles if authoritative and topical, when length is appropriate. Contrary to popular belief, short papers are welcome if falling within the above guide-lines.

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Brain (1989), **112**, 1-38

SEVERE NONFLUENCY IN APHASIA

ROLE OF THE MEDIAL SUBCALLOSAL FASCICULUS AND OTHER WHITE MATTER PATHWAYS IN RECOVERY OF SPONTANEOUS SPEECH

by MARGARET A. NAESER, CAROLE L. PALUMBO, NANCY HELM-ESTABROOKS, DENISE STIASSNY-EDER *and* MARTIN L. ALBERT

(*From the Department of Neurology, Aphasia Research Center, Boston University School of Medicine, and the Boston VA Medical Center, Boston, Massachusetts, USA*)

SUMMARY

The relationship between location and extent of lesion on CT scan and limitation in spontaneous speech was examined. The severity of spontaneous speech ranged from cases with no speech or only verbal stereotypies (first major group) to those with reduced, hesitant, poorly articulated, agrammatic speech (nonfluent Broca's aphasia, second major group). CT scan analysis revealed no *single* neuroanatomical area that contained an extensive lesion which could be used to discriminate the most severe cases from the least severe. The two groups were separable, however, on the basis of the CT scan when the extent of the lesion in *two* subcortical white matter areas were *combined*. (1) the most medial and rostral portion of the subcallosal fasciculus plus (2) the periventricular white matter near the body of the lateral ventricle, deep to the lower motor/sensory cortex area for the mouth

The most rostral portion of the medial subcallosal fasciculus, located in the lateral angle of the frontal horn (extremely deep to Broca's area), contains projections from the cingulate gyrus (area 24) and the supplementary motor area, to the caudate nucleus. We suggest that one explanation for the more severe limitation in spontaneous speech in the first group is the extensive white matter lesion in these two subcortical pathways had interrupted a large number of connections for (1) initiation and preparation of speech movements, and limbic aspects of speech (lesions in the medial subcallosal fasciculus), and (2) motor execution and sensory feedback for spontaneous speech (lesions in periventricular white matter deep to the motor/sensory cortex area for the mouth). Extensive lesion in only one of these two white matter pathway areas, alone was not sufficient to produce long-lasting severe limitation in spontaneous speech and could not be used to discriminate the two groups on the basis of the CT scans. The patients with less severe limitation in spontaneous speech (nonfluent Broca's aphasia) had less extensive lesion within these two white matter areas combined, and had interrupted a smaller number of these subcortical connections. The sites of the lesions in subcortical white matter in CT scans in Broca's original case who could only produce a verbal stereotypy are similar to those in our first group with the most severe limitation in spontaneous speech. The presence or absence of hemiplegia was not related to severity or recovery of spontaneous speech. Careful examination of lesion extent in these two areas of subcortical white matter on CT

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scanning appears to be relevant in predicting potential for recovery of spontaneous speech in some stroke patients.

INTRODUCTION

The anatomical pathways involved in spontaneous speech are not yet well defined, although they have been studied since 1861 when Broca first suggested the importance of the foot of the third left frontal convolution (Broca, 1861*a*, *b*). Aphasic patients with little or no speech or only stereotypies are particularly challenging cases to study from a neuroanatomical perspective. Bonhoeffer (1914) attributed severely limited spontaneous speech in a patient to subcortical lesions that blocked outflow pathways from Broca's area across (1) the anterior corpus callosum and (2) the anterior limb of the internal capsule. More recently, neuroanatomical pathways associated with speech have been examined through the use of CT scans in stroke patients. Most of these studies (Mohr *et al.*, 1978; Brunner *et al.*, 1982; Knopman *et al.*, 1983; Poeck *et al.*, 1984) have focused primarily on the extent of cortical lesions. Research by ourselves and others has shown that damage in subcortical areas can severely limit spontaneous speech (Hier *et al.*, 1977; Naeser *et al.*, 1982; Alexander *et al.*, 1987).

The purpose of this study was to examine more closely the relationship between location and extent of lesion on CT scans, and the severity of impairment in spontaneous speech ranging from no speech or only stereotypies where no meaningful verbal information is conveyed, to nonfluent agrammatic speech (nonfluent Broca's aphasia), where at least some meaningful verbal information is conveyed.

METHOD

Subjects

The study included 27 right-handed patients with aphasia (24 men, 3 women) with a single episode of left hemisphere occlusive vascular stroke (thromboembolic infarct). Their mean age at onset was 57.6 yrs (SD 7.6; range 35-69 yrs). Each patient had a CT scan performed at either the Boston VA Medical Center (Ohio Nuclear Delta 2010 CT scanner) or the Palo Alto VA Medical Center (Syntex System 60 CT scanner). The CT scans were obtained from 2 months to 9 yrs following stroke onset and were produced at 15-35 deg from the canthomeatal line.

The severity of impairment of speech was determined from the elicited spontaneous speech sample for description of the Cookie Theft Picture from the Boston Diagnostic Aphasia Examination (BDAE; Goodglass and Kaplan, 1972). These samples obtained at the latest testing time following stroke onset (6 months to 9 yrs) were used to assign patients to one of four groups (*see* below), based on type and severity of impairment of spontaneous speech. The classification of patients according to severity of impairment of spontaneous speech was carried out independently from the CT scan analysis.

Group 1 (no speech or only a few irrelevant words)

Group 1 consisted of 7 patients (6 men, 1 woman) who were able to produce either no speech or only a few irrelevant words in describing the Cookie Theft Picture (*see* Appendix for speech samples). These patients were tested from 9 months to 8 yrs following stroke onset. Their BDAE auditory comprehension z scores ranged from −0.11 to −1.7 (a moderate to severe deficit, mean −0.91, SD 0.64). Their word repetition ranged from 0–8/10 words (mean 3.7, SD 3.4) and their visual confrontation naming from 0–19/105 (mean 3.6, SD 7.2). Thus not all cases were globally aphasic in all areas of language. (*See also* Table 1.)

Group 2 (only stereotypies)

Group 2 consisted of 10 patients (all men) who were able to provide only stereotypies in describing the Cookie Theft Picture (*see* Appendix for speech samples). These patients were tested from 6 months to 9 yrs following stroke onset. Their BDAE auditory comprehension z scores ranged from +0.09 to −1.95 (mild/moderate to severe deficit, mean −0.80, SD 0.74). Their word repetition ranged from 0–7/10 words (mean 2.2, SD 2.7) and their visual confrontation naming ranged from 0–24/105 (mean 2.8, SD 7.6). This group, like Group 1, included cases who were not globally aphasic in all areas of language (*See also* Table 1.)

Group 3 (a few words and/or some overlearned phrases)

Group 3 consisted of 5 patients (4 men, 1 woman) who were able to provide a few words and/or some overlearned phrases in describing the Cookie Theft Picture (*see* Appendix for speech samples). Their spontaneous speech was more difficult to classify and was considered 'borderline' between the most severe cases in Groups 1 and 2, and the least severe cases in Group 4. These patients were tested from 7 months to 4.5 yrs following stroke onset. Their BDAE auditory comprehension z scores ranged from +0.29 to −2.1 (mild to severe deficit, mean −0.77, SD 0.87). Their word repetition ranged from 0–9/10 words (mean 4.2, SD 4.0) and their visual confrontation naming ranged from 0–42/105 (mean 11.8, SD 17.7). This group was similar to Groups 1 and 2 in that not all cases were globally aphasic in all areas of language. (*See also* Table 1.)

Group 4 (nonfluent Broca's aphasia)

Group 4 consisted of 5 patients (4 men, 1 woman) who were able to provide verbal information relevant to the Cookie Theft Picture with reduced, hesitant, poorly articulated, agrammatic speech (*see* Appendix for speech samples). The test scores for these patients (other than spontaneous speech) were taken from 5 months to 6 yrs following stroke onset. Their BDAE auditory comprehension z scores ranged from +0.93 to +0.38 (only mild deficits, mean +0.69, SD 0.22). Their word repetition ranged from 6–9/10 words (mean 7.8, SD 1.5) and their visual confrontation naming ranged from 58–101/105 (mean 77.8, SD 17.7). This group was milder in all language modalities than the other three groups. (*See also* Table 1.)

When t tests were used to compare BDAE scores among the groups, the patients in Group 4 had significantly higher ($P < 0.005$) auditory comprehension z scores and naming scores than the patients in Groups 1, 2 or 3. In addition, the patients in Group 4 had significantly higher ($P < 0.005$) word repetition scores than the patients in Group 2. There were no other significant differences in auditory comprehension, word repetition or naming among the groups.

Hemisphere asymmetries on CT scans

In order to examine whether the severity of impairment in speech was related to some form of 'anomalous dominance', the occipital and frontal length asymmetries in CT scans were measured using a technique previously published by our laboratory (Pieniadz and Naeser, 1984). When all cases were examined together (n = 27), the distribution of the occipital length asymmetries was as follows: 65% of the cases had the typical left occipital length; 8%, equal and 27%, right. Those 7 patients with atypical right occipital length asymmetry, who may have some form of anomalous dominance (Pieniadz *et al.*, 1983), were distributed evenly across the groups as follows: Group 1,1; Group 2,2; Group 3,2 and Group 4,2.

TABLE 1 PATIENT DATA AND BOSTON DIAGNOSTIC APHASIA EXAMINATION TEST SCORES, GROUPS 1-4

Case	*Sex*	*Age at onset (yrs)*	*CT scan (time post-onset)*	*Occipital length asymmetry*	*Total lesion extent in subcallosal fasciculus plus middle 1/3 PVWM*	*Testing (time post-onset)*	*BDAE auditory comprehension z score*	*Words (72)*	*Commands (15)*	*Word repetition (10)*	*Visual confrontation naming (105)*
Group 1											
1 (S.F.)	F	66	5 mos	L	10	27 mos	−1.60	28.5	2	5	0
2 (L.P.)	M	61	7 mos	R	10	8 yrs	−1.7	30	1	8	6
3 (H.J.)	M	35	9 mos	=	9.95	7 mos	−0.21	51.5	10	0	0
4 (T.F.)	M	65	4 yrs	L	9.25	4 yrs	−1.19	15.5	9	5	0
5 (M.W.)	M	68	2 mos	L	9	2.5 yrs	−0.58	42.5	10	7	19
6 (L.N.)	M	52	16 mos	L	9	15 mos	−1.0	22.5	6	0	0
7 (H.L.)	M	53	9 mos	L	7.98	9 mos	−0.11	60	13	1	0
Group 2											
8 (W.C.)	M	53	3 mos	R	10	3 mos	−1.9	11	4	0	0
9 (D.A.)	M	54	15 mos	L	10	18 mos	−1.34	47	4	0	0
10 (D.E.)	M	56	11 mos	R	10	13 mos	−0.60	53	7	1	0
11 (G.P.)	M	55	9 yrs	L	9.85	9 yrs	+0.05	60	12	5	24
12 (H.M.)	M	58	3 mos	CNM	9.75	8 yrs	−0.90	35	9	5	4
13 (A.G.)	M	64	15 mos	L	8.88	15 mos	−0.94	43	4	0	0
14 (J.N.)	M	53	28 mos	L	8.1	2 yrs	−0.21	50	9	0	0
15 (E.H.)	M	55	7 mos	L	7.88	6 mos	−1.95	13.5	4	4	0
16 (K.M.)	M	59	33 mos	L	7.25	33 mos	−0.33	60	8	0	0
17 (G.J.)	M	59	8 mos	L	7.13	13 mos	+0.09	57	10	7	0
Group 3											
18 (H.D.)	M	63	3 yrs	L	8.73	35 mos	+0.29	57	12	6	42
19 (C.A.)	M	69	5 mos	L	7.43	7 mos	−2.1	10.5	2	0	0
20 (K.W.)	M	61	4 mos	L	6.25	15 mos	−0.90	55.5	5	0	4
21 (A.A.)	M	58	52 mos	R	6	52 mos	−0.70	41	8	9	13
22 (Z.J.)	F	64	11 mos	R	4.25	11 mos	−0.44	57	5	6	0
Group 4											
23 (W.A.)	M	50	44 mos	L	5.88	7 mos	+0.75	66.5	14	9	83
24 (M.E.)	M	58	4 mos	R	5	5 mos	+0.55	60	13	6	62
25 (M.L.)	F	56	16 mos	R	4.75	24 mos	+0.93	71	15	9	85
26 (B.J.)	M	67	12 mos	=	4	17 mos	+0.84	70	15	DNT	101
27 (T.H.)	M	42	6 yrs	L	2.75	6 yrs	+0.38	58.5	12	7	58

The distribution of the frontal length asymmetries was as follows: 36% of the cases had right frontal length, 52%, equal and 12%, left. The 3 patients with atypical left frontal length asymmetry who may have some form of anomalous dominance were distributed evenly across the groups as follows: Group 1,1; Group 2,1; Group 3,0; Group 4,1. This indicates that hemisphere asymmetries were not unusual in each of the groups. It does not appear that severity of impairment in spontaneous speech was related to anomalous dominance as measured by hemisphere asymmetries as demonstrated on CT scanning.

Analysis of CT scan lesion sites

Fig. 1 shows the neuroanatomical areas that were examined by CT scanning for extent of lesion for each patient. The CT scan slice labels B,B/W,W,SM and SM + 1 refer to the Naeser and Hayward (1978) labelling system. Slice B included the following *cortical* areas: Broca's area and the temporal lobe anteroinferior to Wernicke's area. Slice B also included the following *subcortical* areas: the temporal isthmus (Nielsen, 1946; Naeser *et al*, 1982); the insular area, putamen, globus pallidus; anterior and posterior limbs of the internal capsule (ALIC, PLIC); caudate nucleus; subcallosal fasciculus (Muratoff, 1893) and extra anterior lesion extension beyond the frontal horn interrupting fibres of the genu of the corpus callosum (Naeser *et al*, 1982). All these areas are commonly outlined in CT scan atlases (Hanaway *et al.*, 1977; DeArmond *et al.*, 1976; Matsui and Hirano, 1978) or have been discussed in our previous publications on subcortical aphasias (Naeser *et al.*, 1982; Alexander *et al.*, 1987) with the exception of the subcallosal fasciculus (Sc F).

The most medial Sc F is a narrow white matter area surrounding the lateral angle of the frontal horn containing a pathway through which fibres pass from the cingulate gyrus and supplementary

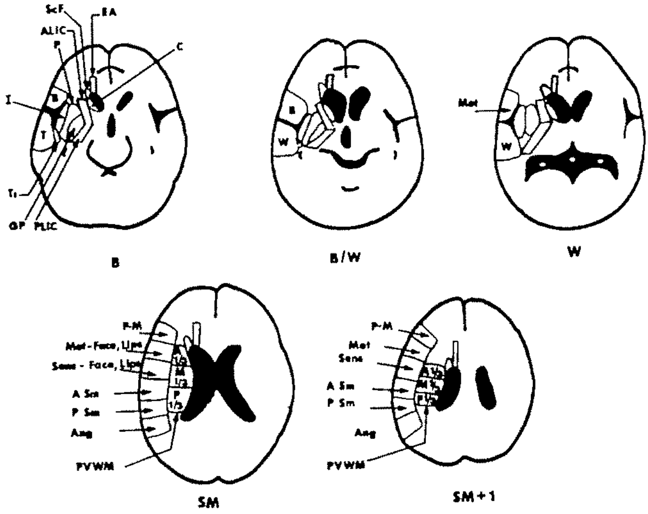

FIG 1. Location of specific neuroanatomical areas on CT scan slices B, B/W, W, SM and SM + 1 (Naeser and Hayward, 1978, slice labelling system). Each neuroanatomical area was examined for extent of lesion using a 0–5 point scale (0 = no lesion; 5 = entire area has solid lesion, *see* text). B = Broca's area (45 on slice B; 44 on slice B/W). T = temporal lobe anterior-inferior to Wernicke's area on slice B, Ti = temporal isthmus, I = insular structures including insula, extreme capsule, claustrum, external capsule, P = putamen, GP = globus pallidus, ALIC = anterior limb, internal capsule, PLIC = posterior limb, internal capsule, Sc F = medial subcallosal fasciculus; C = caudate, EA = extra anterior extension beyond the frontal horn; W = Wernicke's area (22), Mot = motor cortex; P-M = premotor cortex, Sens = sensory cortex; A Sm = anterior supramarginal gyrus; P Sm = posterior supramarginal gyrus; Ang = angular gyrus; PVWM = periventricular white matter area (A 1/3, anterior 1/3 PVWM, M 1/3, middle 1/3 PVWM, P 1/3, posterior 1/3 PVWM)

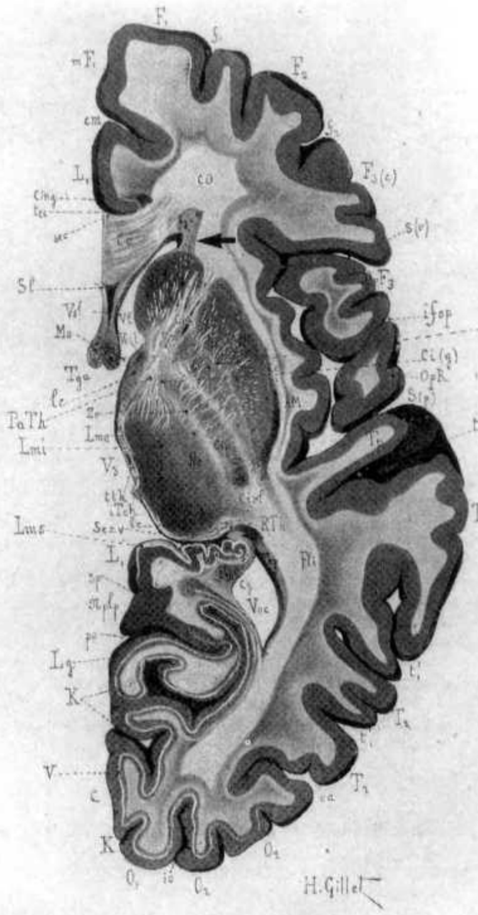

Fig. 225. — Coupe horizontale de l'hémisphère droit, **nº 58**, passant à 58 millimètres au-dessous du bord supérieur de l'hémisphère. Lignes 58 des figures 217 et 218. (Grandeur naturelle.)

FIG. 2. Drawing in horizontal plane from Dejerine (1895, fig. 225), showing location of the medial subcallosal fasciculus, Sc F (substance grise sous-ependymaire) in the lateral angle of the frontal horn (arrow). Note the small size; the width of the medial Sc F is only approximately one-tenth of the distance from the lateral border of the frontal horn to the cortical mantle.

motor area (SMA) to the caudate. The subcallosal fasciculus was first described by Muratoff (1893) in the dog brain as the 'fasciculus subcallosus'. It is located under the corpus callosum. Dejerine (1895) diagrammed it in the human brain and labelled the most medial portion as substance grise sous-ependymaire (Sge, *see* fig. 2). This most medial portion is very narrow and, in fact only one-tenth of the distance from the lateral border of the frontal horn to the cortical mantle. (This represents only a few millimetres on the CT scan.) Yakovlev and Locke (1961) have diagrammed these cingulate and SMA projections to the caudate in more detail in the monkey brain. In their work the most medial portion of the Sc F is labelled stratum subcallosum (St Sbc, *see* fig. 3).

The cortical and subcortical areas examined on slices **B**/**W** (mid-third ventricle level) and **W** (roof of third ventricle level) are similar to most of those examined on slice **B** with the exception of the

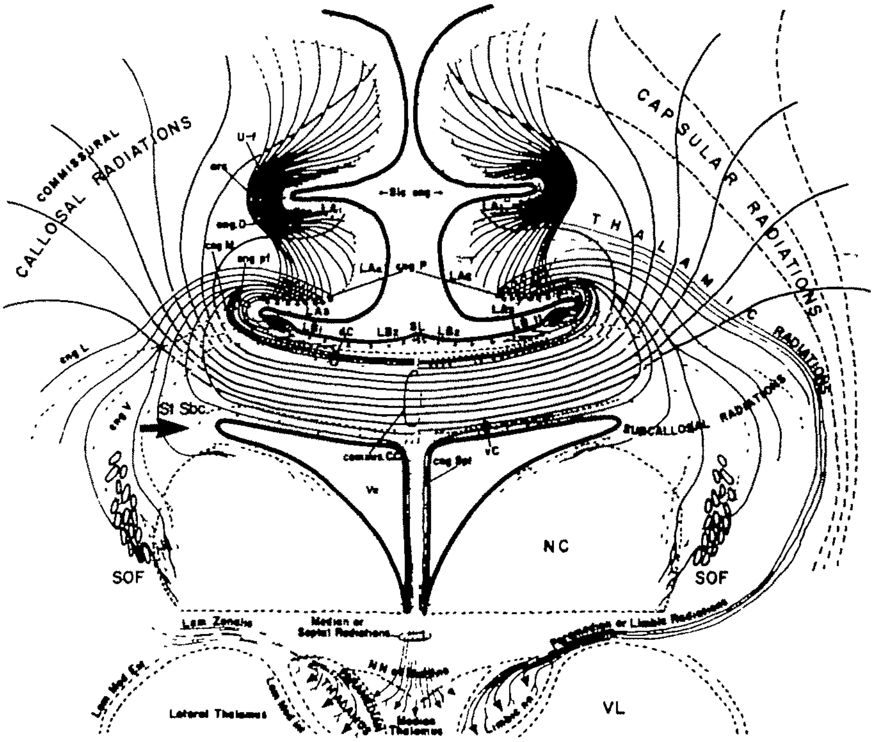

FIG 3. Drawing in coronal plane from Yakovlev and Locke (1961, fig 6), showing location of the medial subcallosal fasciculus (stratum subcallosum St Sbc) in the lateral angle of the frontal horn (arrow) Note that the connections from the cingulate gyrus and supplementary motor area to the head of the caudate are located within the St Sbc area immediately lateral to the frontal horn. (Reprinted with permission)

addition of Wernicke's area on slices B/W and W and motor cortex on slice W; the remainder of the subcortical areas are self-explanatory.

Slice SM (bodies of lateral ventricle level) included the following cortical areas: premotor; motor; sensory; anterior supramarginal; posterior supramarginal; angular. The motor and sensory cortices at this slice level primarily represent the mouth area. Slice SM also included the following subcortical areas: extra anterior lesion extension; Sc F, anterior one-third periventricular white matter (PVWM); middle one-third PVWM and posterior one-third PVWM. Ross (1980) has shown how the descending pyramidal tracts are located immediately adjacent to the body of the lateral ventricle. Thus the deepest periventricular white matter areas, especially the middle-to-posterior one-third PVWM areas contain, in part, these descending pyramidal tract pathways. These PVWM pathways are diagrammed coronally in fig. 4.

The cortical and subcortical areas examined on slice SM + 1 are similar to those examined on slice SM.

Assessment of extent of lesion within each neuroanatomical area

Each neuroanatomical area was assessed visually for extent of lesion within that area using the following scale: 0 = no lesion; 1 = equivocal lesion; 2 = small, patchy or partial lesion; 2.5 = patchy, less than half of area has lesion; 3 = half of area has lesion, 3.5 = patchy, more than half of area has lesion, 4 = more than half of area has solid lesion; 5 = total area has solid

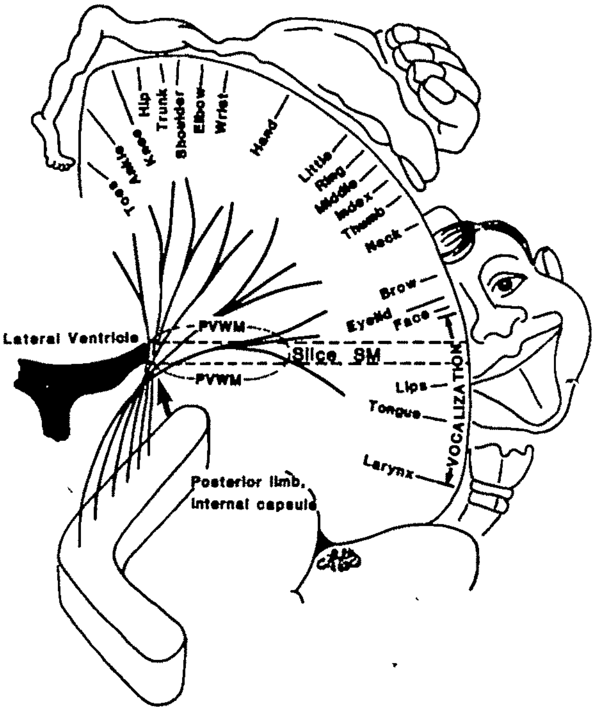

FIG 4. Coronal diagram showing location of descending pyramidal tract pathways in the deepest, subcortical periventricular white matter (PVWM) area immediately adjacent to the body of the lateral ventricle (arrow). On CT scan these descending pyramidal tract pathways are located in the PVWM on slices SM and SM+1. On the CT scan slices inferior to these, the pyramidal tract pathways are located in the posterior limb of the internal capsule (CT scan slices W, B/W and B). *See also* fig. 1

lesion. We have used a similar rating scale in previous CT scan studies with an interrater reliability coefficient of 0.93 (Borod *et al.*, 1984).

The lesion extent data were compared between each group for each neuroanatomical area using Mann-Whitney U tests. These data were compared between each group for each neuroanatomical area on each separate CT scan slice, as well as on combined CT scan slices when a given neuroanatomical area was represented on more than one CT scan slice. For example, Broca's area is represented on slices B and B/W; the extent of lesion in Broca's area was therefore examined on slice B alone, as well as slice B/W alone, as was the mean extent of lesion on slices B and B/W combined.

RESULTS

No significant differences ($P < 0.01$) were observed in lesion site data between the aphasia patients with No Speech (Group 1) versus those with Stereotypies (Group 2). The lesion site data from these two groups were therefore combined, forming a No Speech/Stereotypies Group ($n = 17$) for comparison with the Nonfluent Broca's Group ($n = 5$). (The lesion site data for patients who used only a few words and/or some overlearned phrases, Group 3, are discussed later.)

Significant differences ($P < 0.01$) in extent of lesion were observed between the No Speech/Stereotypies Group vs the Nonfluent Broca's Group for the neuroanatomical areas listed in Table 2. The No Speech/Stereotypies Group always had greater extent of lesion in the specific neuroanatomical areas than did the Nonfluent Broca's Group.

TABLE 2 SIGNIFICANT DIFFERENCES (MANN-WHITNEY U-TESTS, $P < 0.01$) IN LESION SITE DATA BETWEEN THE NO SPEECH/STEREOTYPIES GROUP VS THE NONFLUENT BROCA'S GROUP

Slices B and B/W	*No Speech/ Stereotypies Group*		*Nonfluent Broca's Group*		*P value*
(Mean lesion extent, 2 slices)	X	SD	X	SD	
*Subcallosal fasciculus	4.41	0.81	2.03	1.68	< 0.005
Anterior limb, internal capsule	4.88	0.21	2.5	1.61	< 0.009
Putamen	3.64	1.37	1.2	1.50	< 0.009
Posterior limb, internal capsule	2.40	1.83	0	0	< 0.009
Temporal isthmus	3.69	1.36	0.25	0.5	< 0.0002
Slice W					
Putamen	4.26	1.46	2	1.41	< 0.009
Slice SM					
*Middle 1/3 PVWM	4.71	0.47	2.45	0.87	< 0.0003
Posterior 1/3 PVWM	3.85	1.42	0.4	0.8	< 0.0009
Anterior supramarginal gyrus	3.5	1.92	0.4	0.8	< 0.009
Slice SM+1					
Middle 1/3 PVWM	4.59	0.71	1.78	1.91	< 0.003
Posterior 1/3 PVWM	4.00	1.66	0.8	1.6	< 0.005
Anterior supramarginal gyrus	3.37	1.58	0.2	0.4	< 0.002

Means lesion extent in each area. 0 = no lesion; 5 = total lesion.

* Areas which when summed, produce no overlap between the no speech/stereotypies cases vs the nonfluent Broca's cases.

Each of these areas where significant differences were observed is a subcortical lesion site area with the exception of the anterior supramarginal gyrus area. When the lesion extent values for each individual case were examined in each of these significantly different neuroanatomical areas, there was no single neuroanatomical area which alone could discriminate the 17 No Speech/Stereotypies cases vs the 5 Nonfluent Broca's cases. There were, however, two lesion site areas which, when summed, produced no overlap between the No Speech/Stereotypies cases vs the Nonfluent Broca's cases. These two lesion site areas were subcortical areas including (1) the medial Sc F (mean lesion extent over slices B and B/W) plus (2) the middle one-third PVWM (slice SM). These two areas are shown in the shaded areas in fig. 5. No other lesion site combination could be used to discriminate these 22 cases into their respective groups.

The medial Sc F at slices B and B/W contains the common pathway through which fibres pass from the cingulate gyrus and SMA to the caudate. The middle one-third PVWM at slice SM contains subcortical white matter fibres deep to the lower motor/sensory cortex area for the mouth. In addition, this middle one-third

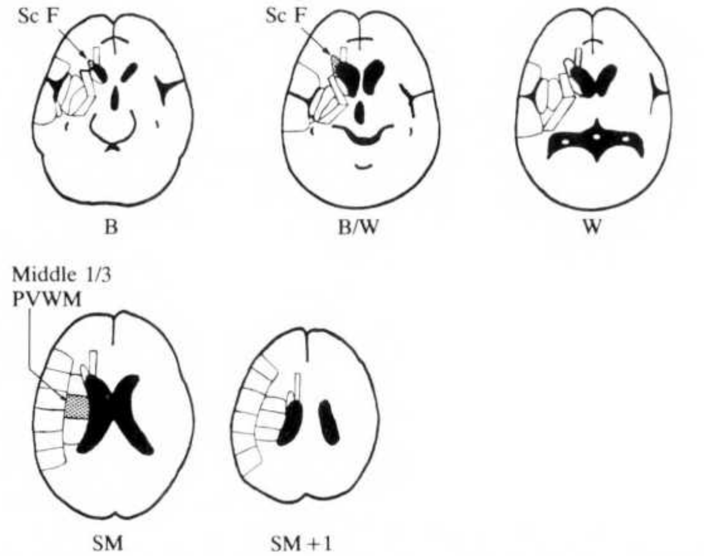

FIG. 5. Location on CT scan slices of the two deep subcortical white matter areas which, when examined for total extent of lesion *combined*, discriminated the cases with no speech or only stereotypies versus those with nonfluent Broca's aphasia. These two deep subcortical white matter areas included (1) the medial Sc F, mean lesion extent at slices B and B/W plus (2) the white matter deep to the lower motor/sensory cortex area for the mouth, the middle one-third PVWM at slice SM.

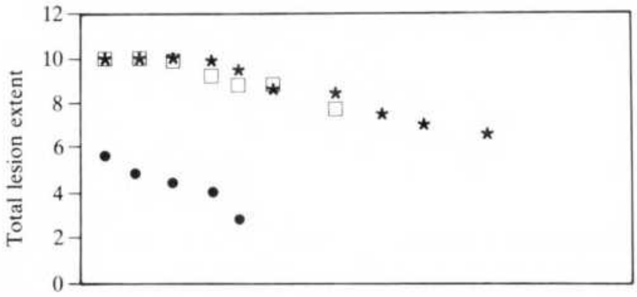

FIG. 6. Values for total lesion extent on the CT scan in the two deep subcortical white matter areas *combined*: (1) the medial Sc F area (mean lesion extent at slices B and B/W) plus (2) the white matter area deep to the lower motor/sensory cortex area for mouth, middle one-third PVWM at slice SM, for individual cases in three groups. Note that all cases with the most severe limitation in speech (Groups 1 and 2) had total lesion extent values above 7; all cases with the least severe limitation in speech (Group 4, Broca's aphasia) had total lesion extent values below 6: The summed maximum lesion extent value of 10 on the graph represents maximum lesion extent ratings of 5 (entire area has solid lesion) in each of the two deep subcortical white matter areas combined. Open squares = no speech; stars = stereotypies; closed circles = nonfluent Broca's aphasia.

PVWM area contains, in part, corona radiata, arcuate fasciculus and additional pericingulate fibres projecting to perisylvian cortical language areas.

The combined lesion extent values for these two subcortical areas are plotted for each No Speech/Stereotypies case and each Nonfluent Broca's case in fig. 6. This graph shows that there was no overlap in these combined lesion extent

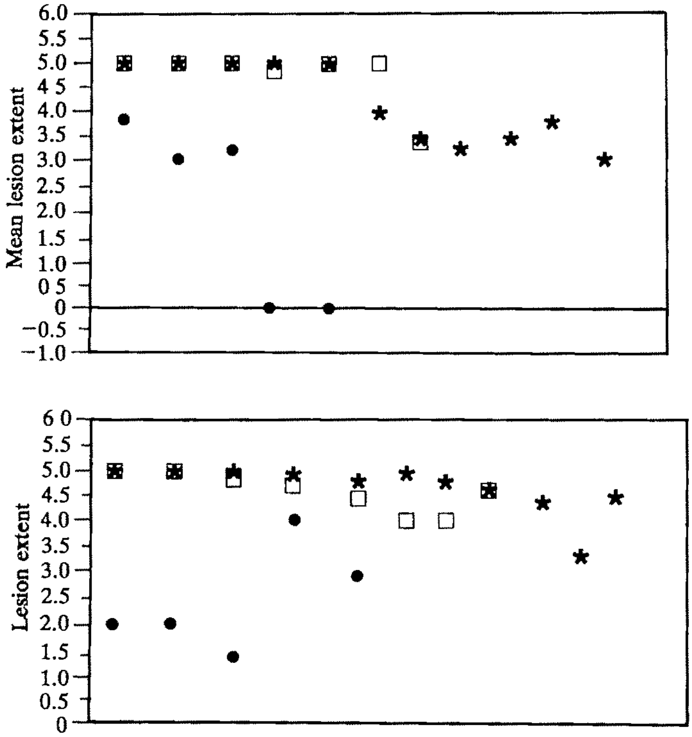

FIG 7. *Top*, lesion extent values *only* in the medial Sc F area (mean lesion extent at slices B and B/W) for individual cases in three groups Note that there was complete overlap in the lesion extent values for the medial Sc F for cases with the most severe limitation in speech (Groups 1 and 2) versus those with the least severe limitation in speech (Group 4, Broca's aphasia) *Bottom*, graph showing lesion extent values *only* in the white matter deep to the lower motor/sensory cortex area for mouth, middle one-third PVWM at slice SM, for the same three groups Note that there was complete overlap in the lesion extent values for the middle one-third PVWM for cases with the most severe limitation in speech (Groups 1 and 2) versus those with the least severe limitation in speech (Group 4, Broca's aphasia). These two graphs show why it is necessary to *combine* the lesion extent values in the two deep subcortical areas mentioned here (*see* fig. 6).

values between the No Speech/Stereotypies cases and the Nonfluent Broca's cases. All the No Speech/Stereotypies cases had summed lesion extent scores above 7 and all the Nonfluent Broca's cases had summed lesion extent scores below 6.

The extent of lesion values in the medial Sc F alone (mean lesion extent values on slices B and B/W) are plotted in the top half of fig. 7 for the No Speech/Stereotypies cases and the Nonfluent Broca's cases. This graph shows that there was overlap in the lesion extent values for the medial Sc F between the two groups; that is, the mean lesion extent values in the medial Sc F alone, were not adequate to discriminate these two very different groups of patients.

The lesion extent values in the middle one-third PVWM alone (white matter deep to the lower motor/sensory cortex area for mouth at slice SM) are plotted in the lower half of fig. 7 for the No Speech/Stereotypies cases and the Nonfluent Broca's cases. This graph shows that again there was overlap in the lesion extent values between the two groups. Thus the lesion extent values in the middle one-third PVWM, alone, also were not adequate to discriminate these two very different groups of patients. It was only when the lesion extent values were combined for these two lesion site areas, medial Sc F at slices B and B/W plus the middle one-third PVWM at slice SM (fig. 6), that the two groups were successfully discriminated on the basis of CT scan lesion extent values.

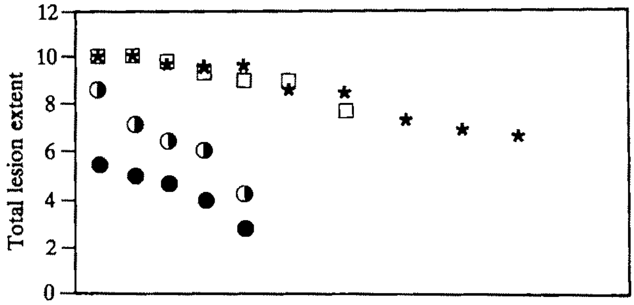

FIG 8 Graph showing total lesion extent values on the CT scan in two deep subcortical white matter areas combined (1) the medial Sc F area (mean lesion extent at slices B and B/W) plus (2) the white matter area deep to the lower motor/sensory cortex area for the mouth, middle one-third PVWM at slice SM, for cases in all four groups. Note that most cases in Group 3, the group with speech which was better than that of the first two groups but worse than that of the fourth, had total lesion extent values which were often between those for the first two groups and the fourth group Open squares = no speech, stars = stereotypies; closed circles = nonfluent Broca's aphasia; half-filled circles = few words, overlearned phrases.

Fig. 8 shows the combined lesion extent values for the two most important areas, medial Sc F area (mean at slices B and B/W) plus the middle one-third PVWM area at slice SM, for all four groups in this study. As mentioned above for fig. 6, this shows that the No Speech/Stereotypies cases had the highest lesion extent values in these two areas combined, and the Nonfluent Broca's, the lowest values. The combined lesion extent values for these two most important areas for the cases in Group 3 (those with a few words and/or some overlearned phrases) basically fell between the combined lesion extent values for the No Speech/Stereotypies cases and those values for the Nonfluent Broca's cases, although a few of these Group 3 cases overlapped into the range for the most severe cases (Groups 1 and 2) and the least severe cases (Group 4). These borderline Group 3 cases are discussed further, below.

The 2 more severe cases in Group 3 (Cases 18, 19) were perhaps 'borderline' in their classification into that group (*see* speech samples in Appendix). These 2 more severe cases in Group 3 also had larger combined lesion extent values for the medial Sc F area plus the middle one-third PVWM area (8.73 and 7.43). These combined lesion extent values overlapped into the range for the No Speech/Stereotypies cases (values above 7).

The least severe case in Group 3 (Case 22) was also perhaps 'borderline' in her classification. Her speech was hesitant, poorly articulated and agrammatic, more compatible with the Nonfluent Broca's Group; however, her comprehension was too severely impaired (BDAE auditory comprehension z score of −0.44 for her to be categorized as having classical Broca's aphasia. The combined lesion extent value for the medial Sc F area plus the middle one-third PVWM area was only 4.25 in this case, a value which overlapped into the range for the Nonfluent Broca's cases (combined lesion extent values below 6).

In summary, the cases with the most severe impairment in spontaneous speech, those with No Speech or only Stereotypies (Groups 1 and 2), had combined lesion extent values for these two areas of above 7, and cases with the least severe impairment, those with Nonfluent Broca's aphasia (Group 4), had combined values of below 6. Those cases who fell between these two groups in terms of severity of impairment of spontaneous speech, namely those with a few words and/or some overlearned phrases, basically fell between these two groups in terms of combined lesion extent values (around 6). There were exceptional cases at either extreme within Group 3. A few sample cases and CT scans from each of the four groups are discussed separately, below.

ILLUSTRATIVE CASES

Group 1 (no speech or only a few irrelevant words)

Case 3

H.J., a 35-yr-old male, at 9 months following stroke onset still had no speech, although he could phonate and produce grunt-like sounds. He had dense right hemiplegia. The CT scan in fig. 9 shows a primarily subcortical infarct which included a large lesion in the medial Sc F at slices B and B/W and large lesion in the middle one-third PVWM at slice SM. The total lesion extent in the two areas combined was 9.95 (*see* fig. 9).

H.J. has subcortical global aphasia and has not previously been reported. The subcortical lesion and spontaneous speech in this case are compatible with our previously published cases of subcortical global aphasia who had lesions in the capsular-putaminal area with anterior-superior lesion extension into PVWM, posterior lesion extension across the temporal isthmus interrupting auditory pathway fibres to the temporal lobe, and extra anterior lesion extension beyond the frontal horn interrupting fibres of the genu of the corpus callosum (Naeser *et al.*, 1982). These cases may have some cortical involvement in the insula, as does this case; however, the recent study by Alexander *et al.* (1987) has shown that cortical lesions in the insula and subjacent white matter produce only a mild conduction aphasia, and are not associated with global aphasia. The spontaneous speech in these subcortical global aphasia cases is not different from those with large cortical/subcortical lesions (*see* fig. 10). This case is a good example of how a small primarily subcortical lesion can produce severe deficits in terms of language behaviour, and that it can be lesion site, not lesion size, which is critical in determining the resultant language behaviour.

Case 4

T F., a 65-yr-old male, at almost 4 yrs postonset, still had no speech and produced only unintelligible speech sounds, e.g., 'juh . . . ah . . . jou . . ', etc. (*see* Appendix). A dense right hemiplegia was present. The CT scan in fig. 10 shows a large cortical/subcortical infarct which included a large lesion in the medial Sc F at slices B and B/W and large lesion in the middle one-third PVWM at slice SM. The total lesion extent in the two areas combined was 9.25 (*see* fig. 10).

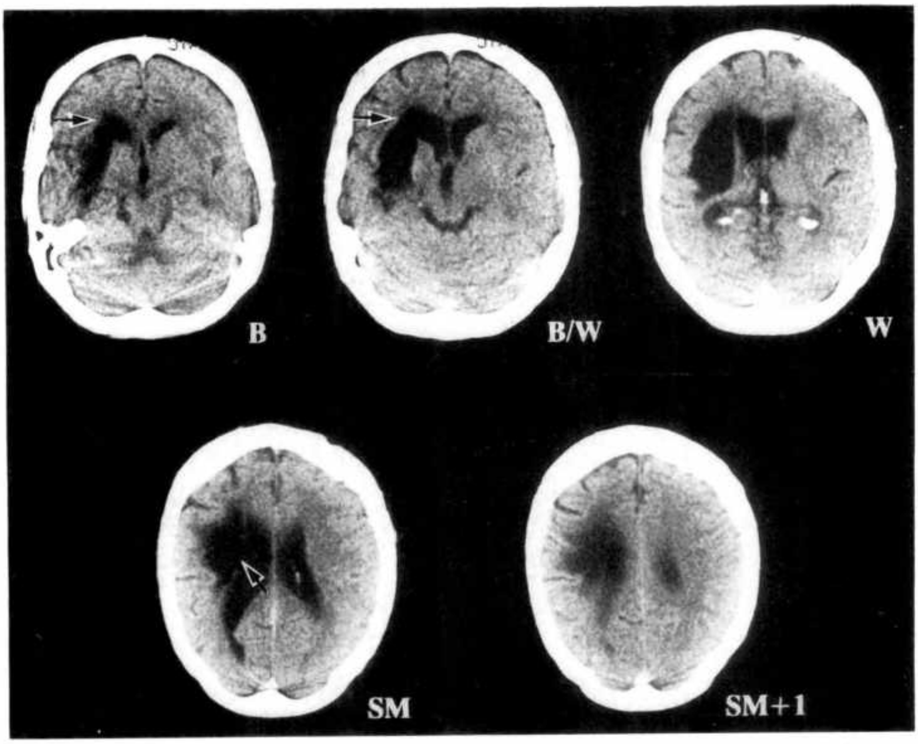

FIG. 9. CT scan at 9 months following stroke onset in *Case 3* (Group 1). A dense right hemiplegia was present. The left hemisphere lesion is on the left side of the CT scan. Lesion extent in the medial Sc F at slice **B** was rated 5; and at slice B/W, also 5 (*see* arrows); mean 5. Lesion extent in the middle one-third PVWM at slice SM was rated 4.95 (*see* arrow); total lesion extent, 9.95. Note that the entire lesion is primarily subcortical.

The cortical/subcortical lesion sites and language behaviour in Case 4 are compatible with previously published cortical/subcortical global aphasia cases (Naeser and Hayward, 1978; Kertesz, 1979; Damasio, 1981; Naeser, 1983). The subcortical CT scan lesion sites in Case 3, fig. 9, can be superimposed over the cortical/subcortical lesion sites in Case 4, fig. 10. Although the cortical lesion in Case 4 increased the overall lesion size, the severity of the deficit in spontaneous speech was equal in both cases. The vascular aetiology in Case 3 was likely to have been an occlusion of the left internal carotid artery (Naeser *et al.*, 1982); that in Case 4 was probably total occlusion of the left middle cerebral artery, including both superior and inferior divisions.

Group 2 (*only stereotypies*)

Case 16

K.M., a 59-yr-old male, at 33 months following stroke onset, could produce only the stereotypy 'morning, morning' or 'boy, boy'. He had only mild incoordination of fine right finger movements, without hemiparesis. The CT scan in fig. 11 shows an extensive lesion in the medial Sc F at slice B, and only a patchy lesion at slice B/W. An extensive lesion was also present in the lateral portion of the middle one-third PVWM (patchy, greater than half of the area affected). The total lesion extent for the two areas was 7.25 (*see* fig. 11).

It is probable that this case had no hemiparesis because the lesion did not extend completely across the middle-to-posterior one-third PVWM adjacent to the body of the lateral ventricle at

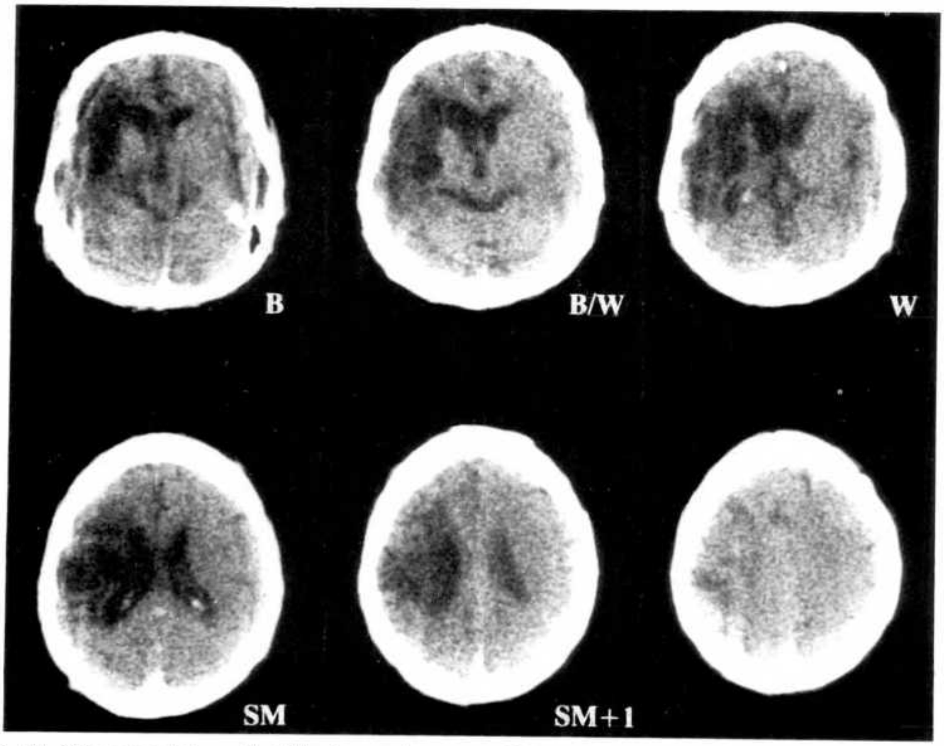

FIG. 10. CT scan at 47 months following stroke onset of *Case 4* (Group 1). A dense right hemiplegia was present. Lesion extent in the medial Sc F at slice B was rated 5; slice B/W, 4.5; mean 4.75. Lesion extent in the middle one-third PVWM at slice SM was rated 4.5; total lesion extent, 9.25. The lesion was a large frontal, parietal, temporal lobe infarct involving cortical as well as subcortical structures in the territory of the entire left middle cerebral artery.

slices SM or SM + 1. The deepest subcortical descending motor pathways were therefore not completely interrupted. Note the depth of the location of the PVWM motor pathways in fig. 4. This case emphasizes the importance of examining the deepest few mm in the PVWM on the CT scan at slices SM and SM + 1 when assessing potential for recovery of hemiplegia. Of course no lesion was present in the PLIC or lower motor pathways on the lower CT slices W, B/W or B, etc. This case makes the important point that the presence or absence of hemiplegia is not always a good prognostic indicator of potential for recovery of spontaneous speech. At almost 3 yrs following stroke onset there was no hemiplegia but he produced no relevant speech.

Case 17

G.J., a 59-yr-old male, at 13 months following stroke onset could only use the stereotypies, '1, 2, 3, 4, 5' or 'boom, boom'. A dense right hemiplegia was present. The CT scan in fig. 12 shows a patchy but definite lesion in the medial Sc F at slices B and B/W and an extensive lesion in the middle one-third PVWM at slice SM. The total lesion extent was 7.13 (*see* fig. 12).

This case exemplifies the necessity of examining extremely carefully the few mm in the lateral angle of the left frontal horn at slices B and B/W. This case had essentially no lesion in Broca's cortical area and the only area where a lesion was present on slices B and B/W included the small

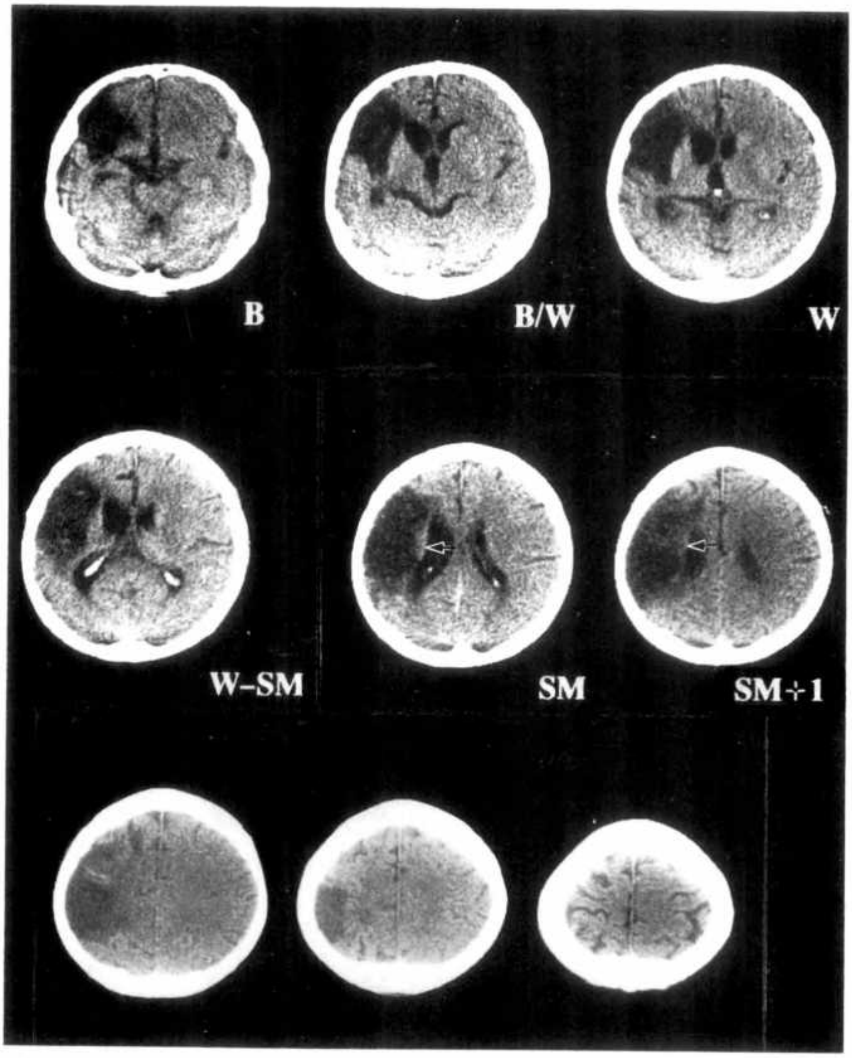

FIG. 11. CT scan at 33 months following stroke onset of *Case 16* (Group 2). No right hemiparesis was present. Lesion extent in the medial Sc F at slice B was rated 5; slice B/W, 2.5; mean 3.75. Lesion extent in the middle one-third PVWM at slice SM was rated 3.5; total lesion extent 7.25. The absence of hemiparesis in this case was compatible with the absence of a lesion in the deepest middle-to-posterior PVWM area adjacent to the body of the lateral ventricle at slices SM and SM + 1 (arrows). This deepest PVWM area contains, in part, the descending pyramidal tract pathways (*see also* fig. 4). No cortical or subcortical lesion was present in arm or leg motor areas near the vertex.

deep subcortical white matter in the area of the medial Sc F, extremely deep to Broca's area, adjacent to the lateral angle of the frontal horn.

Group 3 (a few words and/or some overlearned phrases)

Case 20

K.W., a 61-yr-old male, at 15 months following stroke onset was able to say a few phrases such as 'There, too . . . there too . . . um . . . I don't know . . .', etc. (*see* Appendix). A right hemiplegia

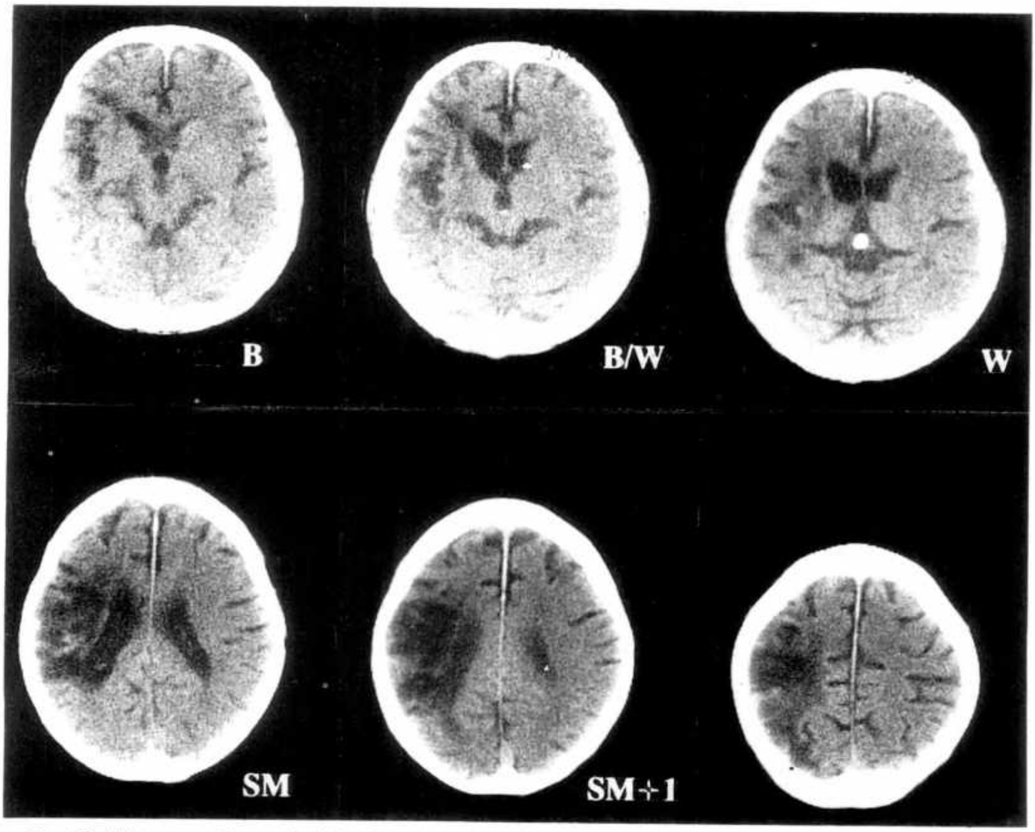

FIG. 12. CT scan at 8 months following stroke onset in *Case 17* (Group 2). A dense right hemiplegia was present. Lesion extent in the medial Sc F at slice B was rated 3.75; slice B/W, 2.5; mean 2.63. Lesion extent in the middle one-third PVWM at slice SM was rated 4.5; total lesion extent 7.13. Note that there was no cortical or immediately subcortical lesion in Broca's area on slices B or B/W.

was present. The CT scan in fig. 13 shows only a partial lesion in the medial Sc F, especially at slice B/W-W and an incomplete lesion (patchy, greater than half of area affected) in the middle one-third PVWM at slice W-SM. The total lesion extent for the two areas was 6.25 (*see* fig. 13).

This is a good example of a case whose speech was between that of the cases in Groups 1 and 2 (no speech or only stereotypies) and that of the cases in Group 4 (nonfluent Broca's) and whose total lesion extent in the two areas also was between that of the other two groups, i.e., Groups 1 and 2, above 7 and Group 4, below 6.

Case 22

Z.J., a 68-yr-old female, at 8 months following stroke onset had speech compatible with nonfluent Broca's aphasia, but too severe a comprehension deficit to be diagnosed as typical Broca's aphasia (*see* Appendix). No hemiparesis was present. The CT scan in fig. 14 shows only a minimal lesion in the medial Sc F at slice B and no lesion in the medial Sc F at slice B/W. In fact, the medial Sc F is elegantly spared at slice B/W, with a solid lesion lateral to it, extending to, and including, Broca's cortical area. A lesion was present in only about half of the middle one-third PVWM area at slice SM-SM + 1. The total lesion extent for the two areas was only 4.25 (*see* fig. 14).

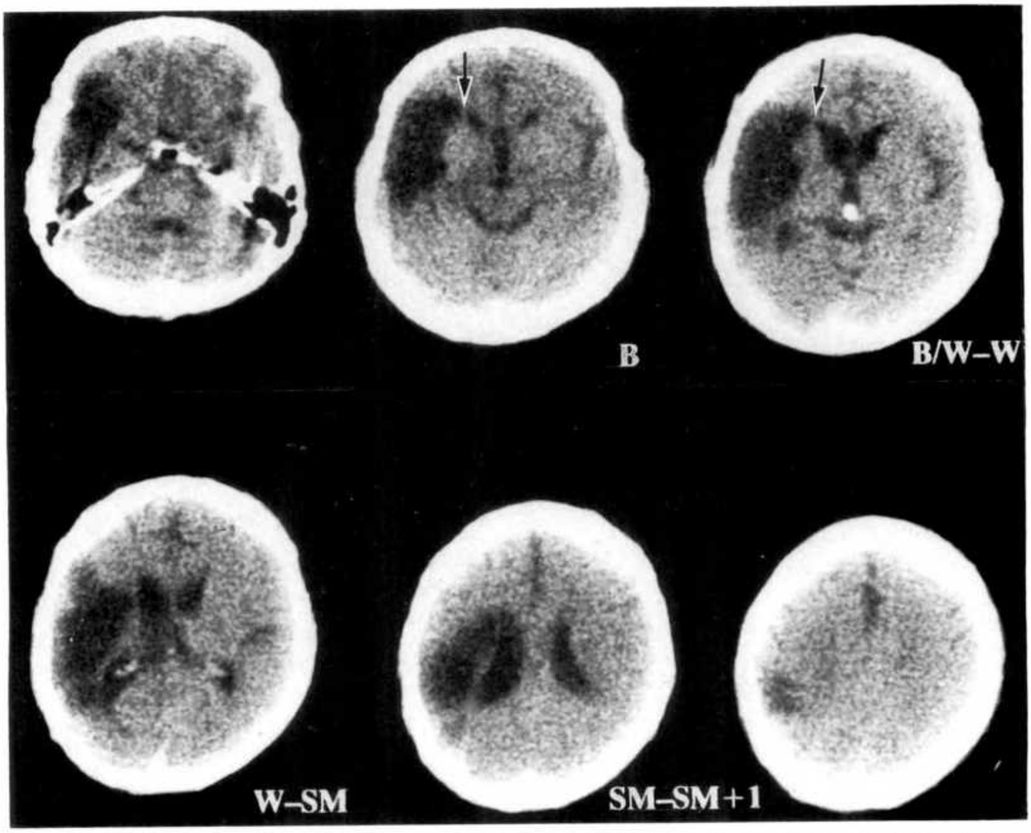

FIG. 13. CT scan at 4 months following stroke onset in *Case 20* (Group 3). A right hemiplegia was present. Note the deep PVWM lesion at slice SM-SM + 1. Arrows show increased sparing in the medial Sc F at slices B and B/W-W. Lesion extent in the Sc F at slice B was rated only 2.5; slice B/W-W, only 2.5; mean 2.5. Lesion extent in the middle one-third PVWM at slice W-SM was rated 3.75; total lesion extent 6.25.

It is probable that this case had no hemiparesis because the lesion did not extend completely across the middle-to-posterior one-third PVWM adjacent to the body of the lateral ventricle at slice SM-SM + 1. The deepest subcortical descending motor pathways were not completely interrupted (similar to Case 16, fig. 11.) Group 2, Case 16, fig. 11, however, had a more extensive lesion in the medial Sc F at both slices B and B/W, than did this Case 22 from Group 3, fig. 14. Case 16 was not hemiparetic, but he produced only stereotypies. Case 22 also was not hemiparetic, and she had nonfluent agrammatic speech which was relevant to the cookie theft picture. These 2 cases differ in lesion site primarily in the deepest subcortical white matter surrounding the lateral angle of the left frontal horn at slices B and B/W, i.e., the medial Sc F at this level (*compare* figs 11, 14).

In summary, Case 22 is important because it shows how close a lesion can be to the border of the lateral angle of the left frontal horn and still spare the medial Sc F (*see* slice B/W) as well as sparing the deeper portion of the middle one-third PVWM area at slice SM, and thus allowing the patient to recover some spontaneous speech. The sparing of the deepest portion of the middle-to-posterior one-third PVWM adjacent to the body of the lateral ventricle at slice SM-SM + 1 is also likely to have spared the deepest descending motor pathways for the arm and leg, so that the patient was not hemiparetic.

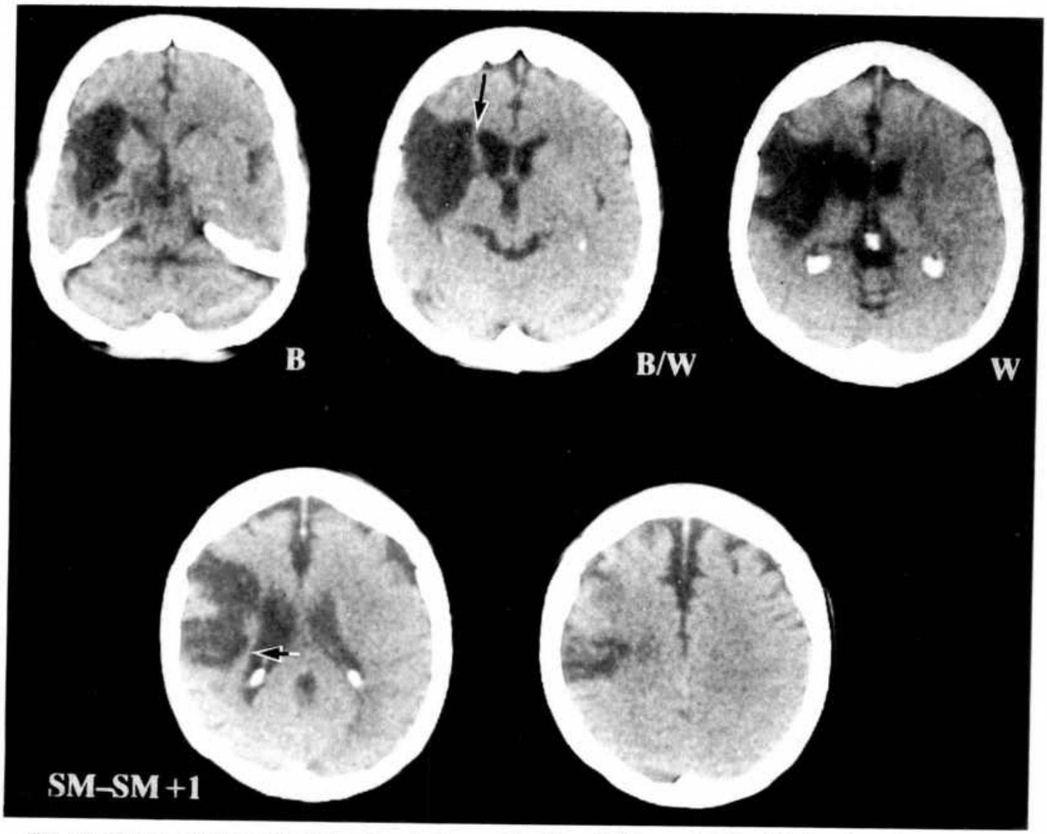

FIG. 14. CT scan at 11 months following stroke onset in *Case 22* (Group 3). No right hemiparesis was present. Lesion extent in the medial Sc F at slice B was rated only 2.5; slice B/W, O; mean 1.25. Arrow shows no lesion in the medial Sc F at slice B/W, despite a large lesion lateral to it, extending outwards to include Broca's cortical area. Lesion extent in the middle one-third PVWM at slice SM-SM + 1 was rated 3; total lesion extent 4.25. The absence of hemiparesis in this case was compatible with the absence of a lesion in the deepest middle-to-posterior one-third PVWM area adjacent to the body of the lateral ventricle at slice SM-SM + 1 (arrow). This deepest PVWM area contains, in part, the descending pyramidal tract pathways (*see also* figs 4, 11).

Group 4 (nonfluent Broca's aphasics)

Case 23

W.A., a 50-yr-old male, at 7 months following stroke onset produced nonfluent agrammatic speech which was compatible with Broca's aphasia (*see* Appendix). A mild hemiparesis was present and there was good recovery. The CT scan in fig. 15 shows that although there was an extensive lesion in the medial Sc F at slices B and B/W, there was only a minimal lesion in the middle one-third PVWM at slice SM (only a small patchy lesion). The total lesion extent in the two areas was 5.88 (*see* fig. 15).

This case has the typical lesion distribution associated with longer-lasting Broca's aphasia which we have repeatedly observed in our laboratory. (The Broca's aphasics who were included in this study were still nonfluent and agrammatic at 7 months to 6 yrs following stroke onset.) This lesion distribution usually includes infarction in parts of Broca's area which extends across to the border of the frontal horn (including medial Sc F, slices B and/or B/W), plus superior lesion extension into

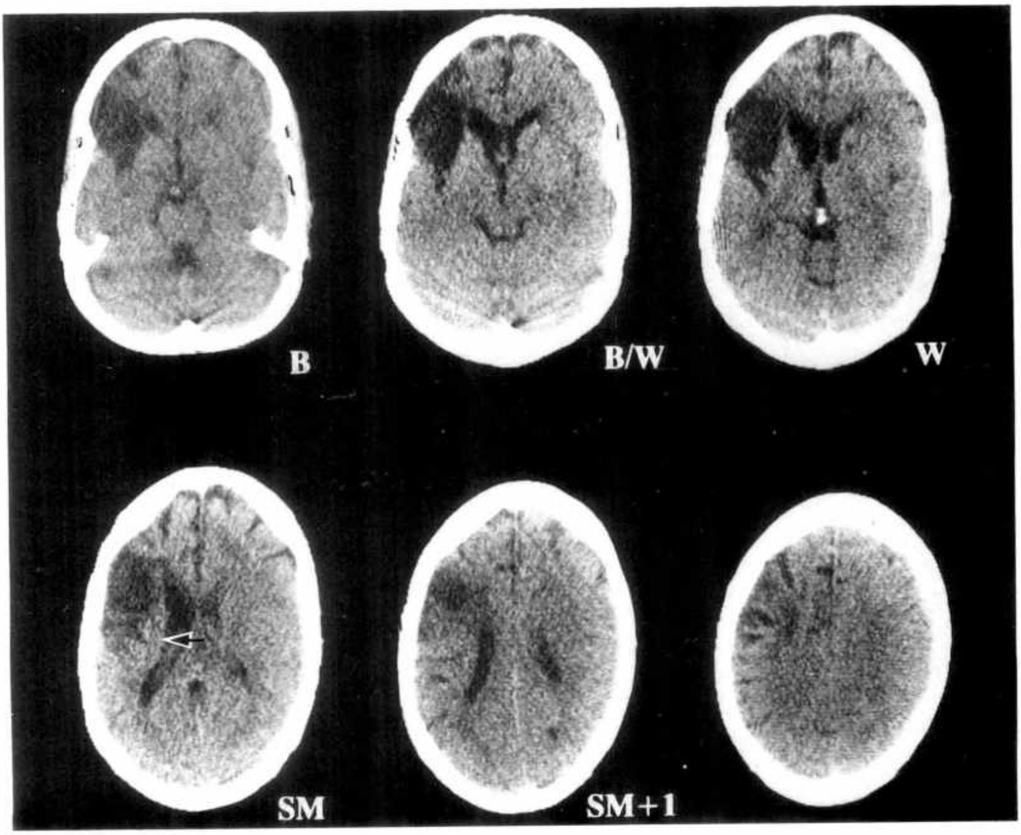

FIG. 15. CT scan at 44 months following stroke onset in *Case 23* (Group 4). A mild hemiparesis was present and there was good recovery. Lesion extent in the medial Sc F at slice B was rated 4; slice B/W 3.75; mean 3.88. Lesion extent in the middle one-third PVWM at slice SM was rated only 2; total lesion extent 5.88. The arrow at slice SM shows a minimal lesion in the middle one-third PVWM which greatly reduced the combined total lesion extent to below 6, a value compatible with his mild limitation in speech. The mild hemiparesis with good recovery in this case was compatible with the smaller lesion in the deepest PVWM area immediately adjacent to the body of the lateral ventricle at slices SM and SM + 1. This deepest PVWM area contains, in part, the descending pyramidal tract pathways (*see also* figs 4, 11, 14).

the lower motor cortex area for the mouth (slices W and SM), which extends into the deep anterior one-third PVWM area, and sometimes part of the middle one-third PVWM area (slice SM). In some cases the lower motor cortex lesion is absent (slices W and SM). The deep subcortical PVWM lesion, however, is usually always present. The cortical portions of this lesion are compatible with lesion sites in longer-lasting Broca's aphasia cases previously published by Mohr *et al.* (1978).

Case 25

M.L., a 56-yr-old female, at 24 months following stroke onset produced nonfluent agrammatic speech compatible with Broca's aphasia (*see* Appendix). No hemiparesis was present. The CT scan in fig. 16 shows a patchy lesion in the medial Sc F at slice B and a more extensive lesion in the medial Sc F at slice B/W. Only a minimal lesion was present in the middle one-third PVWM at slice SM-SM + 1. The total lesion extent value for the two areas was only 4.75 (*see* fig. 16).

This case demonstrates that it is possible to have Broca's aphasia and not have a hemiplegia.

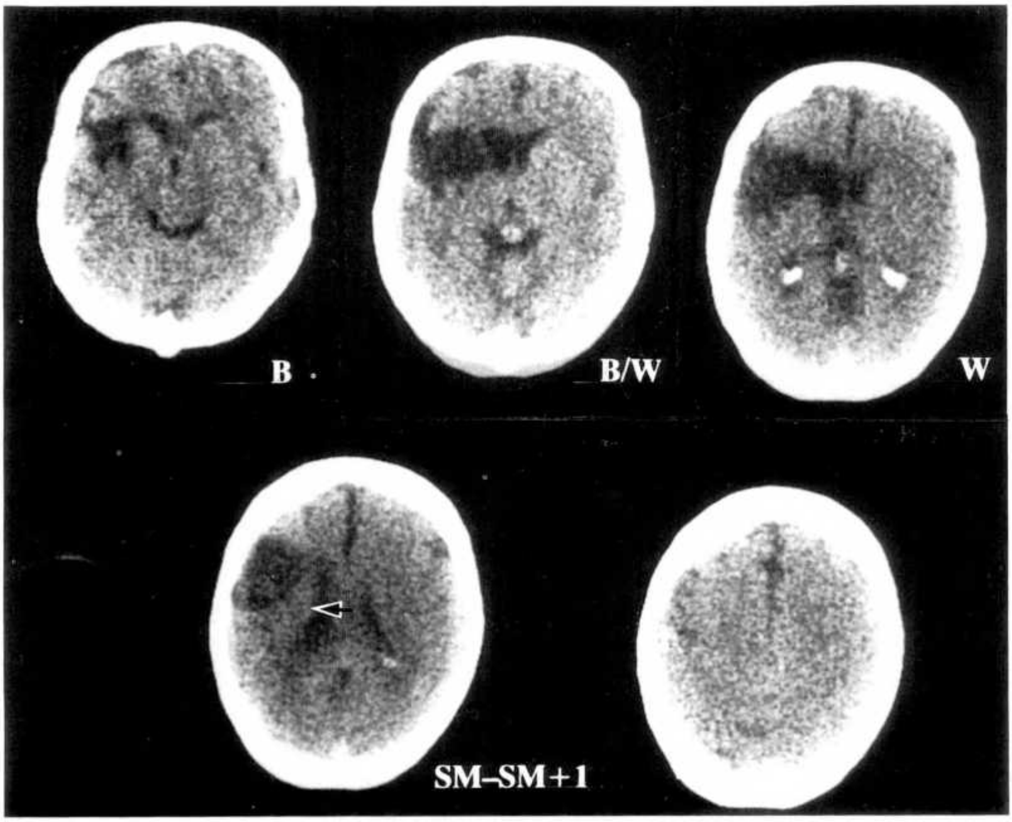

FIG. 16. CT scan at 16 months following stroke onset in *Case 25* (Group 4). No right hemiparesis was present. Lesion extent in the medial Sc F at slice B was rated only 2.5; slice B/W, 4; mean 3.25. Lesion extent in the middle one-third PVWM at slice SM-SM + 1 was rated only 1.5; total lesion extent 4.75. The arrow at slice SM-SM + 1 shows the minimal lesion in the middle one-third PVWM which greatly reduced the combined total lesion extent in this case to below 6, a value compatible with her mild limitation in speech. The absence of hemiparesis in this case was compatible with the absence of a lesion in the deepest middle-to-posterior one-third PVWM area adjacent to the body of the lateral ventricle at slice SM-SM + 1. This deepest PVWM area contains, in part, the descending pyramidal tract pathways (*see also* figs 4, 11, 14).

Again, the lesion did not extend completely across the middle-to-posterior one-third PVWM adjacent to the body of the lateral ventricle at slice SM-SM + 1 so that the deepest subcortical descending motor pathways were not completely interrupted (similar to Case 16, Group 2, fig. 11, and Case 22, Group 3, fig. 14). Each of these 3 cases without hemiplegia had three different types of language involvement. Case 16 could produce only stereotypies; Case 22 could produce nonfluent agrammatic speech but had a moderate comprehension deficit and Case 25 could produce nonfluent agrammatic speech and had good comprehension. All 3 of these cases underscore the point that the presence or absence of hemiplegia is not a good prognostic sign for recovery of speech.

Case 26

B.J., a 67-yr-old male, at 17 months following stroke onset produced nonfluent agrammatic speech which was compatible with Broca's aphasia (*see* Appendix). A dense right hemiplegia was

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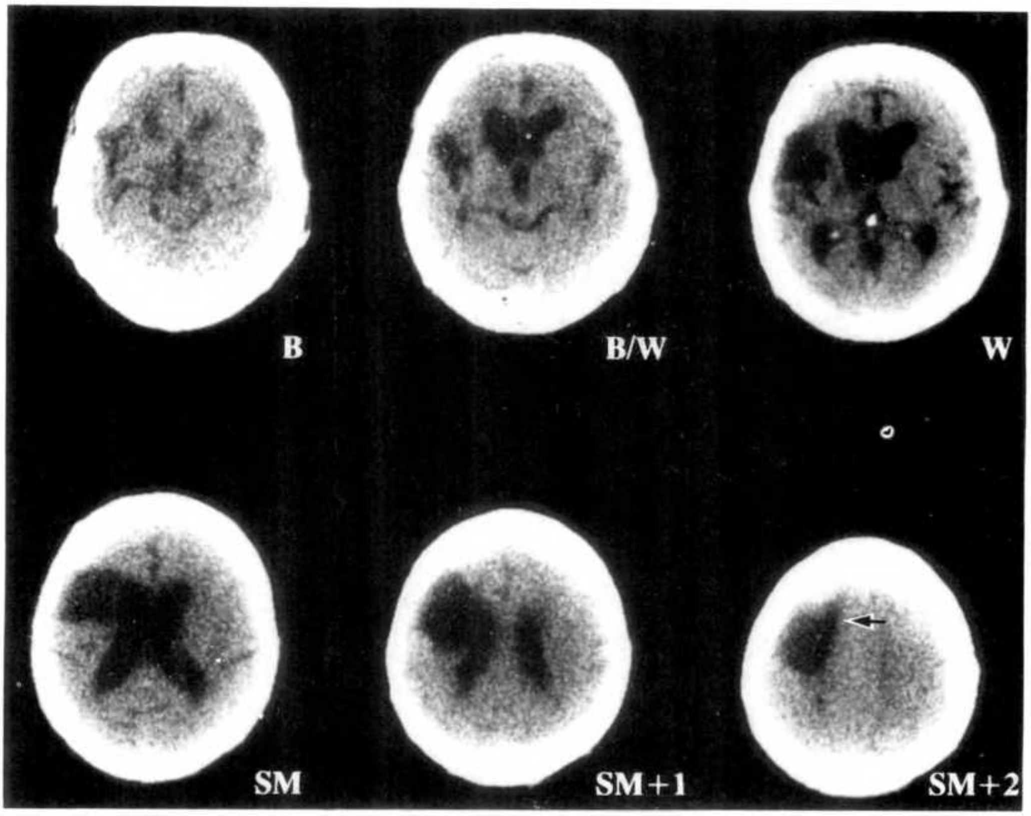

FIG. 17. CT scan at 1 yr following stroke onset in *Case 26* (Group 4). A dense right hemiplegia was present. Note deepest PVWM lesion at slice SM + 1. No lesion was present in the medial Sc F at slices B or B/W, although a lesion was present deep to the supplementary motor area (SMA) and cingulate gyrus on slice SM + 2 (arrow). Lesion extent in the middle one-third PVWM at slice SM was rated 4; total lesion extent, 4. The overall lesion site distribution for this case is unusual as it involves portions of both the distribution of the left middle cerebral artery and the anterior cerebral artery. This case exemplifies how lesion in the middle one-third PVWM can be combined with lesion outside the distribution of the left middle cerebral artery (anterior cerebral artery) to still produce nonfluent, agrammatic speech when there is no lesion in Broca's area and there is no lesion deep to it in the medial Sc F.

present. The CT scan in fig. 17 shows no lesion in the medial Sc F but lesion in greater than half of the middle one-third PVWM area. The total lesion extent was 4 (*see* fig. 17).

This was the only case in this study that had a lesion which included not only portions of the left middle cerebral artery distribution but also portions of that of the left anterior cerebral artery. This case had a lesion at slice SM + 2 which undoubtedly interrupted projections from the SMA and cingulate gyrus to the caudate. Hence, although this Broca's aphasic had no lesion in the medial Sc F or Broca's cortical area, projections for speech initiation, preparation for speech movements and limbic aspects of speech were still interrupted, albeit from a different lesion source (deep to SMA and cingulate gyrus). It is probable that the same pathways were involved in this case, as other Broca's aphasics; however, in this case, the lesion was closer to the origin of the SMA/cingulate gyrus projections rather than being near their more distant projection sites in the medial Sc F deep to Broca's area near the caudate, as seen in most other Broca's aphasia cases.

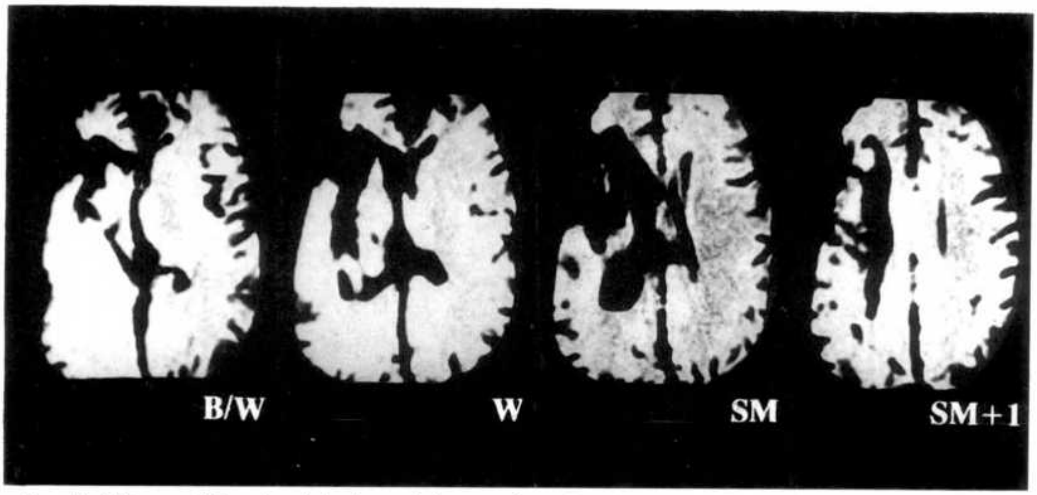

FIG. 18. CT scan of Broca's original case, Leborgne, from Castaigne *et al.* (1980), who at age 51, 21 yrs after stroke onset could produce only the stereotypy, 'tan, tan'. This case was similar to the Group 2 cases in the present study. A dense right hemiplegia was present. Lesion extent in the medial Sc F at slice B/W was rated 5; although slice B was not available, it was assumed that because the lesion was so extensive on slice B/W, it was equally extensive on slice B(5); thus, the mean lesion extent of the medial Sc F was 5. Lesion extent in the middle one-third PVWM at slice SM was rated 4; total lesion extent, 9. This total lesion extent value of 9 in these two deep subcortical white matter lesion site areas was well within the range for cases with severe limitations in speech (total lesion extent values greater than 7). The dense hemiplegia in this case was compatible with a large PVWM lesion which extended to the deepest portion, immediately adjacent to the body of the lateral ventricle, especially at slice SM + 1. (Reprinted with permission.)

Sample cases from previously published studies

Broca's original case, Leborgne

The results from the 27 cases examined in the present study indicate that when a deep subcortical lesion in the medial Sc F at the level of Broca's area is combined with a large lesion in the middle one-third PVWM deep to the lower motor/sensory cortex area for mouth, there is no spontaneous speech or only stereotypies. These results are supported further by examination of the CT scan of Leborgne's brain.

Leborgne was 30 yrs old at the time of his stroke and he died 21 yrs later. His spontaneous speech was limited to the stereotypy 'tan, tan'. His auditory comprehension was reported to be good. He had a dense right hemiplegia. Broca attributed his poor speech to a lesion in the cortical region of the foot of the third left frontal convolution (1861*a*, *b*). Broca himself never observed the depth of the lesion in Leborgne's brain because it was never cut, as was common practice at that time. Recently a CT scan was performed on the preserved brain at 140 yrs post-onset (Castaigne *et al.*, 1980; Signoret *et al.*, 1984; *see* fig. 18).

Fig. 18 shows slices B/W, W, SM and SM + 1 (no slice B was available) of Leborgne's brain. Examination of the deep subcortical white matter surrounding the lateral angle of the left frontal horn reveals an extensive lesion in the medial Sc F at slice B/W. Because the lesion in the medial Sc F is so extensive at slice B/W, it is assumed there was a similarly extensive lesion in the medial Sc F at slice B. There is also an extensive lesion in the middle one-third PVWM at slice SM. The total lesion extent for the two areas was estimated to be 9. At slice SM + 1 the PVWM lesion is contiguous with the lateral border of the body of the lateral ventricle and is compatible with the dense right hemiplegia reported by Broca. (There was no lesion in the PLIC.)

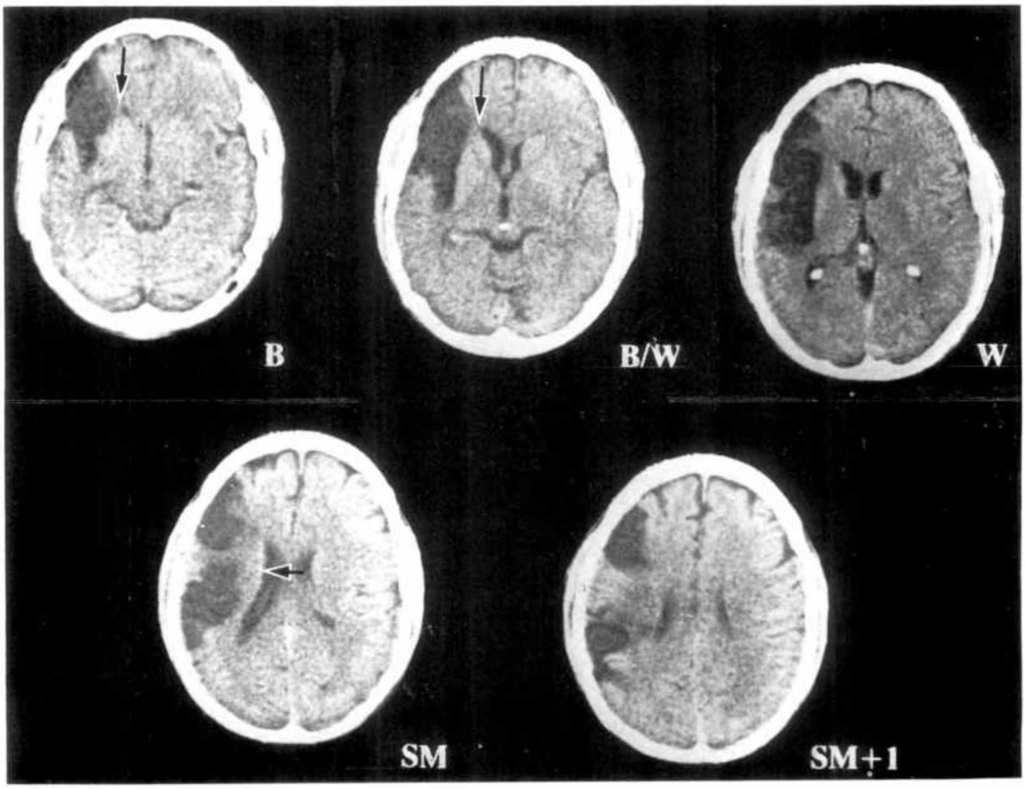

FIG. 19. CT scan at 5 months following stroke onset in *Case 73* from Knopman *et al.* (1983) (fig. 8), who at 6 months after stroke onset produced well articulated, grammatically correct speech. No right hemiparesis was present. Despite a large lesion in Broca's area, surface and deep (slices B and B/W) and a large lesion in the lower motor cortex area for the mouth, surface and deep (slice SM), there was no lesion in the medial Sc F at slices B or B/W (arrows) and there was almost no lesion in the middle one-third PVWM at slice SM (arrow). The absence of hemiparesis in this case was compatible with the absence of a lesion in the deepest PVWM area adjacent to the body of the lateral ventricle at slices SM and SM + 1 (*see also* figs 4, 11, 14, 16). There also appeared to be almost no lesion in the lower sensory cortex area for the mouth. (Reprinted with permission.)

The occipital length asymmetry in Leborgne's CT scan appears to be the typical left occipital length. There appears to be no evidence for any form of anomalous dominance as measured by the CT scan hemisphere asymmetry.

1983 published case

The results from the present study are also supported by a recently published case with good speech recovery by Knopman *et al.* (1983). Their Case 73 supports the findings from the present study because of specific unusual sparing of the two white matter areas outlined here, despite a large extensive cortical/subcortical lesion lateral to these areas. Their case had good recovery of spontaneous speech by 6 months following stroke onset (*see* fig. 19).

The Knopman *et al.* (1983) Case 73 was published as fig. 8 in their paper. This case recovered to scores of 7 on the BDAE in phrase length, grammatical form, articulation and melodic line, by 6 months following stroke onset (D.S. Knopman, personal communication), despite a large lesion in Broca's area, superficial and deep, and a large lesion in the lower motor cortex area for the mouth, superficial and deep. This fluent speech is compatible with the results of the present study because there was sparing of the medial Sc F at slices B and B/W, and most of the middle one-third PVWM at slice SM. The lower sensory cortex area for the mouth also was largely spared. There was no hemiplegia. The PVWM lesion was not adjacent to the body of the lateral ventricle at either slice SM or slice SM + 1.

This case demonstrates that sparing of the medial Sc F at slices B and B/W, and the middle one-third PVWM at slice SM, despite the presence of a large cortical lesion, may be a good prognostic sign for potential for recovery of speech. The sparing of the lower sensory cortex area for the mouth also may have been important for speech recovery.

Speech/language therapy

All the subjects who were inpatients at the Boston VA Medical Center (21/27 cases) received some form of speech/language therapy at the rate of 5 treatments per week while inpatients. Because of the nature of their communicative deficit, a nonvocal therapy programme that trains aphasic patients to produce representational gestures, Visual Action Therapy (VAT) was used with the most severe patients (Helm-Estabrooks *et al.*, 1982) The VAT programme was used with 5/7 cases in Group 1 (no speech); 9/10 cases in Group 2 (only stereotypies) and 3/5 cases in Group 3 (a few words or overlearned phrases). Following successful completion of the VAT programme some of these patients received a course of speech therapy.

One patient in Group 3 was treated with a method called Voluntary Control of Involuntary Utterances (Helm-Estabrooks and Barresi, 1980) which uses oral reading as a basis for gaining control over involuntarily expressed words and phrases. Three out of 5 patients in Group 4 received only Melodic Intonation Therapy (Sparks *et al.*, 1974), a programme for improving spontaneous speech through the use of melodically intoned, rhythmically tapped phrases and sentences. All BDAE test scores reported here are scores obtained following treatment and during the more chronic stage. The exact relationship between the various speech therapy programmes used and final spontaneous speech ability is unknown, and is beyond the scope of this study.

DISCUSSION

Other CT scan studies of severe limitation in spontaneous speech

CT scan studies of lesion sites producing severe limitation in spontaneous speech were undertaken recently by Brunner *et al.* (1982) and by Poeck *et al.* (1984). Brunner *et al.* concluded that automatisms and recurring utterances occurred only with combined cortical and basal ganglia lesions. No specific subcortical white matter pathway areas, such as the medial Sc F, were examined in that study. Composite lesion diagrams were shown only for one CT scan slice (slice W) and no complete CT scans of individual cases were shown. Although the information provided was limited, it appears that the conclusions from that study are not in agreement with our findings, which suggest that it is involvement of primarily *subcortical white matter* pathways (not basal ganglia and cortical lesions) which produce severe limitation in spontaneous speech.

Poeck *et al.* (1984) specifically examined patients with only stereotypies as compared with other global aphasics and found no differences in CT scan lesion sites between the two groups. The results of our study are in agreement with their study in that no differences were observed in lesion sites between the cases who produced only stereotypies versus those who had no speech. Poeck *et al.*, however, also found no difference in lesion sites between cases with only stereotypies versus those with other forms of aphasia, including 'Broca's, Wernicke's, transcortical sensory, left middle cerebral artery occlusion and isolated basal ganglia lesions'. That investigation used a technique of superimposing lesions to search for common lesion sites; no specific subcortical pathways such as the medial Sc F were examined. They concluded that superimposing lesions is not an adequate approach and recommended that future anatomical studies attempt to examine disconnections involving critical cortical areas.

Two subcortical white matter pathway areas identified in the present study

The present study focused on specific cortical and subcortical areas and isolated two subcortical white matter pathway areas which, when damaged, resulted in severe limitation in spontaneous speech, that is, no speech or only stereotypies. These two areas, namely (1) the medial Sc F surrounding the lateral angle of the most rostral portion of the frontal horn (CT scan slices B and B/W) and (2) the white matter deep to the lower motor/sensory cortex area for mouth (CT scan slice SM), are discussed in more detail, below.

The Sc F, as mentioned above, was first described by Muratoff in 1893 in the dog brain. Rose (1935) cites four different labels for this area of white matter, comprising those of Muratoff, the fasciculus subcallosus, Anton, the fasciculus longitudinalis medialis, Wernicke, the fasciculus nuclei caudati, and Dejerine, the fasciculus fronto-occipitalis. In Dejerine's 1895 text, the most medial portion of the Sc F is labelled substance grise sous-ependymaire (Sge) and the more lateral portion, fasciculus occipito-frontalis (OF) (fig. 2). In the Yakovlev and Locke's (1961) study with the monkey brain, it is labelled stratum subcallosum (fig. 3).

Benjamin and Van Hoesen (1982), using horseradish peroxidase injections in monkey brains, have shown strong reciprocal connections between area 24 of the cingulate gyrus and the SMA. The importance of the SMA in 'the development of the intention-to-act' has been reviewed by Goldberg (1985). Barnes *et al.* (1980), using autoradiography in monkey brains, have shown that a major entry point for direct projections from the cingulate gyrus (and indirect projections from the SMA due to strong cingulate-SMA reciprocal connections) to the caudate is in the most medial white matter surrounding the lateral angle of the frontal horn in its most rostral portion. Jürgens (1984) has also observed direct connections from the SMA to the caudate. These mesial frontal cortex projections then spread to the ventral and lateral portion of the caudate and to the lateral portion of the putamen. Hence lesions located in the most medial white matter surrounding the lateral angle of the most rostral portion of the frontal horn (medial Sc F) would be interrupting pathways from the cingulate gyrus area and SMA leading into the caudate and putamen. This would have an effect on the initiation, preparation for speech movements, and limbic aspects of spontaneous speech.

The Sc F actually has projections from the cingulate and SMA to the caudate throughout the inferior portion of the corpus callosum. It appears, however, that it is the most medial and rostral of these connections which are relevant in severely limiting speech when combined with a lesion deep to the lower motor/sensory cortex area for the mouth. In the present study, significant differences in lesion extent in the medial Sc F were only observed between the No Speech/Stereotypies group versus the Nonfluent Broca's group on the lower CT scan slices (B and B/W; CT scan slices at the level of Broca's area), not the higher CT scan slices, W, SM or SM + 1, although clearly the medial Sc F is also present in the lateral angle of the frontal horn and body of the lateral ventricle on these higher CT slices (*see* fig. 1).

Yakovlev and Locke (1961) further studied two parts of the Sc F: (1) the medial division containing corticostriate fibres from the cingulum and (2) the lateral division containing corticocortical fibres of the superior fronto-occipital bundle. It appears that lesions in the most medial portion of the Sc F (i.e., the portion interrupting the corticostriate projections) produce the most severe limitation in spontaneous speech only when combined with white matter lesions deep to the lower motor/sensory cortex area for the mouth (middle one-third PVWM at slice SM).

Additional support for the importance of the most medial white matter area surrounding the lateral angle of the left frontal horn in relationship to spontaneous speech comes from stimulation studies in this area performed by Van Buren (1963, 1966). During surgical procedures for basal ganglia disorders, it was observed that lower range electrical stimulation within or in the vicinity of the head of the caudate nucleus consisted predominantly of speech arrest; patients ceased counting. In 7/10 cases there was speech arrest from stimulation on the left, in 3/10 cases, from the right side. There also was arrest of voluntary movement.

Van Buren (1963) wrote '. . . what has been produced by stimulation in the vicinity of the head of the caudate nucleus is not indeed aphasia, but a more basic disturbance in which the impulse to speak or to continue another task has been dulled or forgotten'. He further described the response as that which resembles most closely the response obtained from the SMA.

It is still not known why the patients in this study who had extensive lesions in the most medial and rostral portions of the Sc F, plus lesions in the white matter deep to the lower motor/sensory cortex area for the mouth, had no speech or only stereotypies. We suggest, however, that each lesion in each subcortical white matter area produced important disconnections. The Sc F lesion interrupted projections from the cingulate and SMA to the striatum. Thus, this lesion appears to have interrupted initiation, preparation for speech movements, and limbic aspects of speech. The lesion in the subcortical white matter deep to the lower motor/sensory cortex area for the mouth may have interrupted the pathways necessary for motor execution as well as possibly those pathways necessary for sensory feedback. Hence we hypothesize that lesions in these deep subcortical areas effectively prevented any relevant speech because there were no available pathways for speech initiation, motor execution or sensory feedback. Undoubtedly, other language association areas were also disconnected as a result of lesions in these two white matter areas.

When a large lesion was present in *both* the medial Sc F and the white matter deep to the lower motor/sensory cortex area for mouth, spontaneous speech pathways were essentially disconnected in the left hemisphere, and the patient either had no speech or only stereotypies (*see* figs 9, 10, 11, 12, 18.) In 1 case, this severe limitation persisted for at least 9 yrs following stroke onset (Case 11). In patients where nonfluent agrammatic speech was present, there was more sparing of either one of these two subcortical white matter pathway areas. Usually it was the extra sparing of the subcortical white matter deep to the lower motor/sensory cortex area for the mouth (middle one-third PVWM at slice SM) which was associated with improved speech ability resulting in nonfluent agrammatic speech (*see* figs 14, 15, 16). When both of these two subcortical areas were completely spared, despite a large cortical lesion lateral to them including Broca's area and the lower motor cortex area for mouth, there was normal phrase length, grammatical form, articulation and melodic line (*see* fig. 19.)

Importance of the combination effect of these two subcortical white matter areas

It is important to stress the *combination* effect of lesion in these two subcortical areas in relationship to severe limitation in spontaneous speech. Previous research in our laboratory and others has shown that small lesions in the frontal lobe alone, including subcortical lesions involving white matter lateral to the frontal horn, will produce only transcortical motor aphasia (Freedman *et al.*, 1984). The medial Sc F has not been specifically mentioned in earlier reports on transcortical motor aphasia, but interruption of pathways from the SMA has been implicated in the poor initiation of speech observed in this form of aphasia (Rubens, 1975).

Alternatively, it has been our observation that patients who have a lesion which is limited to the subcortical PVWM area at slice SM and/or slice SM+1 may have only mild transcortical motor aphasia with or without dysarthria, and with or without hemiplegia, depending on the exact location of the PVWM lesion along the lateral border of the body of the lateral ventricle (Freedman *et al.*, 1984; Alexander *et al.*, 1987; Alexander and Naeser, 1987; Naeser, Alexander, Stiassny-Eder *et al.*, unpublished observations).

Lesion in these two white matter areas are contiguous, and additional lesions vary

Although the results of this study have focused on subcortical lesions in the medial Sc F and in the white matter deep to the lower motor/sensory cortex area for the mouth, it should be stressed that obviously the lesions in these two areas are contiguous and many other pathways are also undoubtedly disconnected along with these lesions. These other disconnected pathways may include portions of the fronto-occipital connections in the lateral bundle of the Sc F, frontopontine connections, portions of the arcuate fasciculus, and/or other pericingulate projections to the perisylvian language areas. The exact course of the lesion between the most medial and most rostral portion of the Sc F on slices B and B/W to and including parts of the middle one-third PVWM deep to the lower motor/sensory cortex area for the mouth on slice SM, varied from case to case and not all of them included the ALIC, caudate or putamen, for example. All cases did, however, also include the anterior one-third PVWM at slice SM. Variations in lesion direction as well as individual variation in exact location of anatomical areas will, of course, contribute to variations in the language behaviour and perhaps also to potential for recovery. In addition, although the role of the right hemisphere for spontaneous speech is limited and not well understood at this time, this is another variable which must be considered and may contribute to individual variation.

Presence or absence of hemiplegia not associated with recovery of spontaneous speech

Recent studies have suggested that the absence of hemiplegia with acute global aphasia may be a favourable prognostic sign for good recovery from global aphasia (Legatt *et al.*, 1987; Tranel *et al.*, 1987). The results from the present study, however, suggest that absence of hemiplegia is not always a valuable prognostic sign in predicting recovery of spontaneous speech. One case in the present study had no hemiplegia, but also still had no speech almost 3 yrs post-stroke. This case and others examined in our laboratory have suggested that the presence or absence of hemiplegia may be independent of the type or severity of aphasia. Hemiplegia which occurs with lesions in middle cerebral artery territory without involvement of the PLIC appears to be directly related to whether the lesion is in the middle-to-posterior one-third PVWM and whether the lesion is immediately adjacent to the body of the lateral ventricle at slices SM and/or SM + 1.

Subcortical aphasia studies and refinement of subcortical anatomical lesion site labels

The overall mechanism underlying severe and lasting aphasia in cases with subcortical lesions is receiving increasing attention (Crosson, 1985). The importance of subcortical lesions in the striatum and surrounding white matter in producing atypical ‘subcortical’ aphasias has been stressed by Damasio *et al.* (1982), Naeser *et al.* (1982), and Alexander *et al.* (1987). Although the small, deep subcortical white matter pathway of the medial Sc F had not been isolated for specific examination per se in our previous studies on subcortical aphasia (Naeser *et al.*, 1982; Alexander *et al.*, 1987), it was included in those studies, in part, under the anatomical label ‘extra anterior lesion extension’ (EALE) beyond the frontal horn. A subcortical lesion in this area was always seen in the most severe cases with little or no speech, although at that time it was assumed that this lesion was interrupting connections across the corpus callosum to the right hemisphere as had been suggested by Bonhoeffer (1914).

The results from the present study suggest, however, that it is connections from the cingulate and SMA to the caudate which were actually interrupted and hence, initiation and preparation of speech movements were also interrupted. In fact, EALE beyond the frontal horn was not an important lesion site which distinguished severe versus milder limitation in spontaneous speech in the present study, although it still may have interrupted projections across the corpus callosum to the right hemisphere in cases where this lesion was present. Results from the present study suggest that it is the most medial white matter which is immediately lateral to the frontal horn (not the white matter which is immediately anterior to the frontal horn) which is the most critical area to assess in evaluating the extent of lesions within the medial Sc F.

Problems with composite lesion site methodology

The methodology used in the present study was unique in that it did not rely on composite lesion sites. Instead, our approach focused on the potential effect of disconnection in specific anatomical pathways. Previous studies which had tried to examine composite CT scan lesion sites in association with severe limitation in spontaneous speech did not obtain meaningful results (Brunner *et al.*, 1982; Poeck *et al.*, 1984). Indeed, if we reexamine our own composite lesion site drawing for 'anterior' capsular/putaminal (C/P) subcortical aphasia cases (fig. 4, Naeser *et al.*, 1982), it appears these cases with grammatical but dysarthric speech had extensive lesions in *both* the medial Sc F *and* the middle one-third PVWM.

When each 'anterior' C/P subcortical aphasia case is examined separately, however, there is variable amount of lesion extension in the medial Sc F lesion and middle one-third PVWM lesion. For example, in a given case, if greater lesion extent is present in the first area, then lesser lesion extent is present in the second area, and vice versa. The individual case in fig. 2, bottom (1982) shows no lesion in medial Sc F at slice B, an extensive lesion in medial Sc F at slice B/W, and a partial lesion in the middle one-third PVWM at slice SM. This variability in lesion extent between the two areas can never be appreciated in a composite lesion site drawing for *all* the cases with the same language behaviour, but different extents of lesion in the two areas. The lesion extent in separate areas must be examined separately, for each individual case, even if the language behaviour is the same. Undoubtedly several different lesion site combinations can produce similar language behaviour.

Two subcortical white matter areas hypothesized to affect specific cortical areas

It is hypothesized from cerebral blood flow studies (Olsen *et al.*, 1986) and positron emission tomography studies (Kushner *et al.*, 1984; Metter *et al.*, 1985) that subcortical white matter lesions have a direct effect on specific cortical areas which have become indirectly involved due to lesions in the subcortical connections to those specific cortical areas. In patients with small subcortical lesions which do not interrupt critical pathways to or from specific cortical areas, there is often recovery, especially when good collateral flow is present (Olsen *et al.*, 1986). None of the subcortical cases in this study, however, had good recovery. Hence it is assumed that the severe cases in this study who even had small subcortical lesions, but which were located in critical areas (most medial and rostral Sc F plus white matter deep to the motor/sensory area for the mouth) probably had a lesion in white matter pathways which were critical for cortical activation of speech. Thus although the emphasis in this study was on the examination of *subcortical* lesion sites, it was probably the *cortical* pathways which were disconnected by the subcortical lesions, which ultimately produced the severe limitation in spontaneous speech. Future research with PET or rCBF with patients with infarcts in the most medial and rostral portion of the Sc F and white matter deep to the motor/sensory cortex area for the mouth may help to clarify exactly which cortical areas have been disconnected.

Our hypothesis at this time is that at least the cingulate gyrus/SMA cortical area as well as the motor/sensory cortical area for the mouth are two important cortical areas involved in spontaneous speech. In addition, other perisylvian cortical language areas must also be considered such as Broca's or Wernicke's areas and/or the supramarginal gyrus area. The importance of both the cingulate gyrus/SMA as well as the lower motor/sensory cortex for the mouth in spontaneous speech is supported both by the rCBF studies of Larsen *et al.* (1978) and by the electrical stimulation studies of Penfield and Roberts (1959).

Additional neuroanatomical evidence which supports our findings comes from a recent study by Jürgens (1982). He injected horseradish peroxidase into the cortical larynx area within the lower sensorimotor face cortex in 3 squirrel monkeys. He observed retrogradely labelled cells in a continuous band extending all along the upper bank of the sylvian fissure from a homologous Broca's area rostrally, to the parietal association cortex (area 7) caudally. 'In addition, labelled cells were found in the ventrolateral prefrontal cortex, orbital cortex, *anterior cingulate gyrus, supplementary motor area*, insula and inferior temporal gyrus' (p. 377) (italics added by the present authors). In addition, labelled cells were observed in many subcortical nuclear groups. The results of the Jürgens' study thus are particularly relevant to the present study, because he stressed that 'The two medial cortical areas found . . . to contain labelled cells thus must be regarded as the limbic and SMA representation of the face' (p. 383). In his conclusions he stressed that these strong connections between the anterior cingulate gyrus/SMA and the cortical larynx area support previous observations that the anterior cingulate gyrus/SMA is extremely relevant to spontaneous speech disturbance in man (Penfield and Roberts, 1959; Larsen *et al.*, 1978). Hence this recent study by Jürgens (1982) is indirectly supportive of the importance of the two subcortical white matter areas isolated as important in spontaneous speech in the present study (medial Sc F and middle one-third PVWM deep to face area); and directly supportive of the two cortical areas implied to be important in spontaneous speech in the present study (cingulate gyrus/SMA and lower motor/sensory cortex area for mouth).

The present study focused on spontaneous speech and although all cases in

Groups 1 and 2 had severe limitation in spontaneous speech, not all of these cases had complete cessation of speech; 10/17 cases in Groups 1 and 2 could still repeat a few words and 4/17 could correctly name some pictures to visual confrontation. Research by Kirzinger and Jürgens (1982), as well as others (Smith *et al.*, 1981) has shown that lesions in the SMA have a direct effect on the initiation of 'spontaneous' motor behaviour patterns which are triggered internally and not on those triggered directly by external stimuli. Kirzinger and Jürgens observed, for example, that after the SMA was ablated in squirrel monkeys and these monkeys were placed in isolation, the number of vocal 'isolation calls' emitted from the monkeys was reduced, although the acoustic structure remained intact. Thus the absence of internally-generated speech (spontaneous speech) in the presence of some externally-generated speech (word repetition and naming) may be compatible, in part, with lesions directly affecting projections from the SMA. Further, variation in word repetition and naming ability observed across those subjects who otherwise had no meaningful spontaneous speech may have been due, in part, to variation in the extent of the lesion in the projections from the SMA, as well as from other areas. This would require further study.

Use of CT scanning to predict potential for recovery of spontaneous speech

Examination of the two subcortical white matter areas isolated in this study is suggested as a basic starting point for assessing potential for recovery of spontaneous speech in severely nonfluent stroke patients with infarction in the various branches of the left middle cerebral artery. When working with patients who have lesions outside the distribution of this artery, especially in the left anterior cerebral artery, different structures must be examined. For example, in cases with left anterior cerebral artery infarcts, it is possible that cortical lesions in the SMA and/or the cingulate gyrus may combine with subcortical lesions in the middle one-third PVWM to produce long-lasting impairment in speech, even when no lesion is present in the medial Sc F at slices B and B/W. Obviously, other cortical and/or subcortical lesion sites may also combine to produce equally severe limitation in spontaneous speech.

After completing this study with 27 cases, we recently reviewed over 50 other cases in our files and did find 1 case of exceptional recovery in spontaneous speech, despite an extensive lesion in the medial Sc F at slices B and B/W and in the middle one-third PVWM at slice SM (*see* fig. 20). The total lesion extent for these two structures in this case was 7.37, a value which should have placed him in Groups 1 or 2 (values above 7). The patient was a 45-yr-old, right-handed male who was a highly successful lawyer at the time of his stroke. At 1 yr post-stroke, he was able to use 7-word phrases, although they were spoken very slowly and with poor articulation. For example, in describing the cookie theft picture, he said, in part, '. . . she is going du get wet feet because . . . hu . . . uh . . . is going to get . . . the shoe is going to get wet'. He has continued to recover in spontaneous speech until the present (over 5 yrs post-stroke), although the slow rate

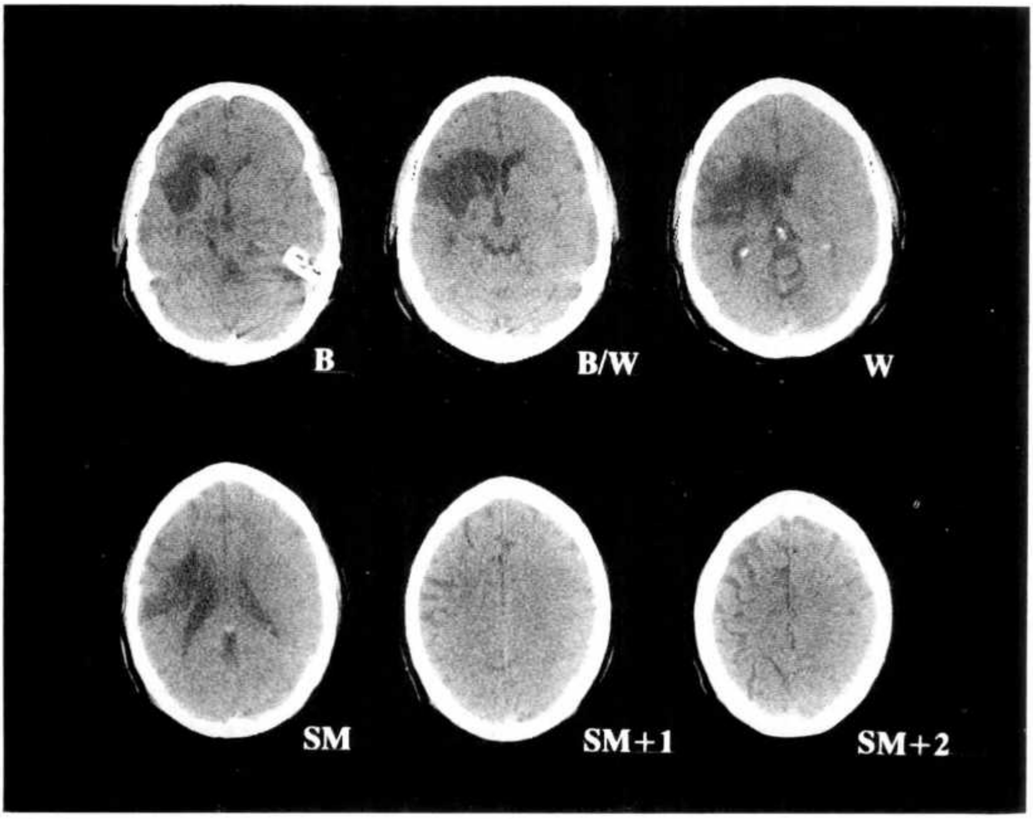

FIG. 20. CT scan at 1 yr following stroke onset in a case who had unexpected recovery of spontaneous speech at 1 yr post-stroke (*see* text) despite an extensive lesion in the medial Sc F (slice B, 3.75; slice B/W, 5) and the middle one-third PVWM at slice SM (4). The total lesion was rated 7.37. A dense right hemiplegia was present.

articulation have persisted. A dense right hemiplegia is still present. This case exemplifies the fact that exceptions will always be found for patterns of language recovery that are unexpected with specific CT scan lesion sites. In this case, although the combined lesion extents placed him in the range for cases with the most severe limitation in spontaneous speech, his speech exceeded that for even the Broca's aphasics in Group 4. His exceptional recovery may have been related to a relatively young age at onset, a higher educational level and a higher premorbid IQ.

Lastly, examination of the two subcortical white matter areas stressed in the present study may contribute to a better understanding of the mechanisms involved in normal spontaneous speech. In the rCBF studies by Larsen *et al.* (1978), significant increases in blood flow were observed, particularly in the left hemisphere, in the SMA and the motor and sensory cortex area for the mouth during automatic speech. Results from the present study have suggested some specific subcortical white matter pathways, which although not visible in rCBF studies which focus on cortical cerebral blood flow, appear to be critically important in the final coordinated cortical activation for speech.

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APPENDIX

Case	*Time post-onset*	*Spontaneous Speech Samples for description of the Cookie Theft Picture*
Group 1		
1	27 mos	'Yeah . . . yeah'
2	8 yrs	No speech
3	9 mos	No speech
4	47 mos	'Juh . . . ah . . . jou . . . juhjuh . . . uhpai . . . uhnouer'
5	2.5 yrs	No speech.
6	15 mos	'No . . .' (and 'grunts')
7	9 mos	No speech.
Group 2		
8	6 yrs	'Boom . . . boom'
9	18 mos	'Ai . . . da tu . . . dididi'
10	13 mos	'Senny fenny'
11	9 yrs	'I don't know . . . good good . . . yes, yes . . . tu, tu . . . no, no'
12	4 yrs	'Wa, wa . . . for Christ sake'
13	15 mos	'Guhdi, guhdi . . . wazuh waz'
14	2 mos	'Bee bee . . . bye bye'
	(2 yrs)	At this time there was almost no speech
15	6 mos	'Yes, yes'
16	33 mos	'Morning, morning . . . boy, boy'
17	13 mos	'1, 2, 3, 4, 5 . . . boom, boom'
Group 3		
18	35 mos	Unintelligible vowel sounds. 'Siuhl . . . yeah down . . . un . . . cookies wash um um wash eeah no water here, fuhee, no good over here.'
19	7 mos	'Goddam . . . Chrissakes . . . I forgot it . . . well goddam'
20	15 mos	'There, too . . . there, too . . . um . . . I don't know . . . that's all I guess gee whiz. I don't know, that's all . . . well . . . that, too and there and there'.
21	52 mos	'Well . . . uh . . . Duh um . . . glasses . . . run'
22*	8 mos	'Nothing. The kid break'in an . . . on an that one. He gonna get gett'in, gah. Its running He given one to give one. She's dissing.'
Group 4		
23	7 mos	'The wady is doing her dishes. Sink undis over uh . . . The window is open and the "w" won . . . a very funny day outside . . . ook children . . . a boy and a girl'.
24	7 mos	'A kids . . . a cookies . . . and uh, uh, fall down, . . . wash'in de dishes . . . uh runn'in water . . . fish fash . . . uh foor . . . he was . . . girl a cookie'.
25	24 mos	'The girl . . . uh, sh-sh sheez, the boy fall down . . . the ch-ch chair . . . the boy . . . is . . . cookies . . . the boy, the lady . . . is . . . raiping the dishes'.

*At this time the patient's speech output was almost compatible with nonfluent Broca's aphasia, however her comprehension was still too impaired for her to be considered a Broca's aphasic

APPENDIX

Case	*Time post-onset*	*Spontaneous Speech Samples for description of the Cookie Theft Picture*
Group 4 (*cont.*)		
26	17 mos	'Well, wiss . . . watcheez, water, . . . uh, this kaitee jar . . . uh . . . do . . . eee . . . dee . . . deezeez . . . uh, ahniz . . . ahniz, uh, whoops . . . bay . . . birl . . . no . . . girl . . . boy . . . girl, I /ton/ know'.
27	6 yrs	'Dis iz . . . bee out a lawn built up . . . This kid . . . fall down . . . This kid waking up here'.

Brain (1989), **112**, 39-63

READING WITH ONE HEMISPHERE

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SUMMARY

The subjects of this study were 2 originally right-handed teen-aged girls who had undergone complete hemispherectomy (1 left, 1 right) for intractable epilepsy. Both subjects had developed normal language and reading capacities before the onset of their illness. The reading performance of H.P. (whose right hemisphere had been removed), while not as advanced in level as that of a normal 17-yr-old, showed no abnormality in any subcomponent of reading skill. The reading performance of N I. (whose left hemisphere had been removed) was poor, but with a pattern of retained and impaired subskills strikingly similar to adult deep dyslexic patients and to split-brain patients given reading tasks lateralized to the left visual field (right hemisphere) The results are discussed with regard to implications for the reading capacity of the nondominant right hemisphere and also its putative contribution to normal reading

INTRODUCTION

The vast majority of right-handed people have left hemisphere (LH) dominance for language skills such as reading. It is an unresolved question, however, whether the right hemisphere (RH) of a LH-dominant individual also develops significant capacity for reading. There are two approaches to this question, and several sources of evidence within each. The first approach assesses reading performance when the RH must function predominantly on its own. Pertinent sources of evidence include: (1) patients with extensive LH lesions resulting from stroke or other cerebral lesion; (2) patients with surgical separation of the hemispheres who are given language input restricted to the RH; and (3) patients who have had the LH surgically removed for intractable epilepsy and/or progressive brain disease.

The second approach assesses the contribution of the RH to normal reading performance. One possible source of evidence here involves split-field presentation of written language to normal subjects; and many interesting results have emerged from the use of this paradigm (e.g., Hardyck *et al.*, 1985; Young and Ellis, 1985). However, while adequately controlled studies can ensure that material presented in the left visual field arrives initially in the RH, it is difficult both to control and

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to ascertain the locus of subsequent processing in subjects with two intact and connected hemispheres. Therefore one turns to neuropsychological evidence derived from the same three types of clinical populations, but now on the right side: the reading performance of adults with RH lesions, of split-brain patients given right visual field input, and of patients with right hemispherectomy. The logic of this approach is that, if the RH normally makes a significant contribution to skilled reading, then a person forced to rely exclusively or primarily on the LH should read abnormally.

With so many sources of evidence germane to this issue, why does it remain controversial? The answer, of course, is that none of the sources is unimpeachable. With both split-brain and hemispherectomy cases, the majority of patients have had congenital or early brain abnormalities, probably resulting in atypical lateralization of language functions (Rasmussen and Milner, 1977). This problem does not afflict interpretation of adult stroke patients. On the other hand, such patients with LH lesions virtually never have total LH destruction, leaving the question as to whether their residual language abilities derive primarily from the damaged LH or from the intact but linguistically inadequate RH (*see* Lambert, 1982, for further discussion of the difficulties inherent in these various sources of evidence).

The most compelling source of evidence on the question of RH reading would be provided by cases of hemispherectomy for brain disease with a late onset, after normal lateralization would be expected to have occurred. Such cases (e.g., Smith, 1966) are extremely rare, and were mainly studied before current standards for detailed and theoretically informed assessment had emerged. The exceptions are the hemispherectomy cases, one right and one left, extensively and elegantly studied by Zaidel (1977; 1978*a*, *b*; 1980; 1982). However, as age at onset of symptoms in these 2 cases was 6:7 and 7:8, respectively, these patients may still have been within a period of relative plasticity (although there is considerable controversy surrounding this notion, which will be addressed further in the Discussion). Furthermore, while Zaidel's case of left hemispherectomy is assuredly relevant to the question of language processing in the RH, she had essentially no reading ability (e.g., Zaidel, 1978*b*). Thus, apart from marking the lower end of its range, she cannot inform us about the particular linguistic skill of interest here.

The present study reports the reading performance of 2 hemispherectomy patients, one left and one right, with normal early development followed by onset of brain disease at approximate ages of 13 and 10 yrs. The framework guiding this investigation is the cognitive neuropsychological approach applied in recent years to the study of acquired reading disorders such as surface dyslexia (Patterson *et al.*, 1985) and deep dyslexia (Coltheart *et al.*, 1980). Indeed, deep dyslexia, first investigated in detail by Marshall and Newcombe (1966, 1973), is particularly germane to the current investigation. Deep dyslexic patients (most of whom have suffered large infarcts in the territory of the left middle cerebral artery) show a complex pattern of reading impairments including a total failure to pronounce even the simplest printed nonsense words (e.g., CAG); a considerable advantage in oral word reading for concrete, imageable nouns (e.g., CHICKEN) relative to either abstract nouns (e.g., CONTEXT) or grammatical words such as prepositions (e.g., AT, OF, BY); and a tendency, in single word oral reading, to produce error responses with a semantic (but no orthographic or phonological) resemblance to the target word (e.g., HERMIT—'recluse').

This pattern of acquired dyslexia is relevant in view of a suggestion by Coltheart (1980, 1983) and Saffran *et al.*, (1980) that deep dyslexic reading is most plausibly and economically understood as reading with the RH. This hypothesis has been subject both to support (e.g., Zaidel and Schweiger, 1984) and criticism (e.g., Warrington, 1981). Since neither the RH hypothesis of deep dyslexia nor any contending hypothesis has been able to give a wholly adequate account of the observed pattern of performance (*see* Coltheart *et al.*, 1987), the issue remains unresolved. This theoretical debate adds another focus of interest to our case of indisputable RH reading.

CASE REPORT

Case 1 (N.I.)

Until the onset of her illness at the age of 13 yrs, N.I. (born 1969) was a normal, right-handed girl, attending secondary school with performance in the average range, and with no personal or family history of neurological abnormality. In September 1982, she presented with a generalized convulsion preceded by lethargy and episodes of dysphasia for 6 weeks. Over the next 4 months she had further generalized attacks, one of these followed by transient weakness of the right-sided limbs. In May 1983, some 8 months after the first generalized convulsion, focal motor attacks involving the right arm and leg appeared, and within weeks these became epilepsia partialis continua. Attacks lasted 30–40 s and were generally preceded by an unpleasant taste in the mouth. On examination 1 yr after the onset of the illness, N.I. had a right hemiparesis (grade 4), an extensor right plantar response, a right homonymous hemianopia, and some dyspraxia. She had become left handed and was sufficiently disabled that she had to hold on to furniture to move around.

From the outset the attacks included dysphasia. Although speech and language functions were frequently interfered with as a result of the seizures and postictal states, N.I.'s speech only deteriorated radically some 14 months after the onset of her illness.

Diagnostic tests had consistently implicated N.I.'s left hemisphere. Electroencephalography (EEG) showed widespread LH abnormalities. Although CT scans initially did not indicate any gross changes, within 18 months postonset they reflected evidence of LH atrophy The preoperative scan showed moderate left hemiatrophy with an area of low density in the left posterior region of an apparent ischaemic origin.

Preoperative psychometry showed scaled scores of (1) on both the vocabulary and comprehension subtests and scaled scores of (4) and (1) on block design and object assembly subtests of the WISC-R (Wechsler, 1976). Administration of the Schonell Graded Word Reading Test (Schonell, 1942) indicated a reading age of 6:5. Auditory comprehension for single words as measured by the British Picture Vocabulary Scale (Dunn and Dunn, 1982) was at the age level of 5:5.

A sodium amytal test (Branch *et al.*, 1964) was carried out preoperatively to determine whether N.I.'s RH was capable of subserving gross speech and memory functions. Injections were given on two separate days, and the LH was injected three times, the RH once. The evidence derived from these tests was inconclusive, but speech arrest coincident with the onset of hemiparesis was only evident when the right cerebral hemisphere was inactivated.

Before operation N.I. was having continuous seizures. She had a moderate expressive dysphasia, a complete right homonymous hemianopia, a right facial palsy, grade 2 cortical weakness of the right upper limb with no useful movement in the hand, and similar weakness of her right lower limb. She had cortical sensory loss involving the whole right side of the body, and increased tendon jerks and an extensor plantar response on that side.

A total left hemispherectomy using Adam's modification (Adams, 1983) was performed in 1985, 30 months after the onset of N.I.'s illness. The postoperative diagnosis was 'Rasmussen's encephalitis' (Rasmussen, 1978, 1983). This is a syndrome whose aetiology is obscure. It invariably begins in childhood or early adolescence, and is characterized by the onset of unilateral focal motor seizures followed by a progressive hemiparesis. The neuropathological features include widespread cortical lesions of an 'ischaemic' type, of variable size, and perivascular cuffing with inflammatory cells. It is this latter feature that has led to the use of the term 'encephalitis', although no aetiological agent has ever been implicated and the CSF during the illness shows no inflammatory changes. Histopathology in N.I. showed widespread abnormalities affecting the left neocortex. Major structural landmarks were either shrunken because of neuronal cell loss or grossly distorted as a result of the disease process.

Seizures were totally arrested following the operation and N.I. has remained seizure-free to date. She is still on a moderate dose of anticonvulsants. Her neurological state has remained unchanged. She has been attending a nonacademic college where she spends her time learning to cook and to do handicrafts.

N.I.'s spontaneous speech is very limited both in content and grammatical form, perhaps more anomic than classically agrammatic. Here is a sample of her speech, in conversation with one of the authors:

> K.P.. What do you particularly like to eat? N I.· I like . . . er . . . you know . . . the . . . I can't say it now . . . well, I like   I don't like chips a lot but . . I like Bolognaise. K.P. Do you cook? N.I : Yes. K P · What do you cook? N I · Different things. I made . . . er . . . I made . . . these (pointing to the apple that she was eating). But not that . . these. . . K.P.· What did you do with them? N.I.. Crust over the top. K.P.: What's that called? N.I.. An apple. K.P.. Yes, that's an apple, but with the crust over the top, what do we call it? N.I.. I can't remember. K.P. An apple   . N.I Pie!

Case 2 (H P.)

H.P. was the product of a normal pregnancy and delivery. Shortly after her birth in 1970, she was diagnosed as suffering from Turner's syndrome. This chromosomal abnormality is not generally associated with intellectual deficit (Menkes, 1980), and indeed H.P. went on to develop normally and to achieve appropriate developmental milestones. She was right handed, and her early years were medically unremarkable. She attended a normal school locally and was performing in the above average range in all academic subjects until her epilepsy commenced When she was nearly 10 yrs old, she was found totally unresponsive, lying on her left side with her eyes closed. A month later, a similar episode occurred, and over the ensuing months a pattern of minor seizures changed to focal attacks involving the left limbs. The severity of these increased such that within months she was admitted to hospital with epilepsia partialis continua and a moderate Todd's paralysis.

A CT scan carried out at this stage indicated some right cerebral atrophy. The EEG showed multifocal discharges maximal in the right rolandic region. The sleep EEG showed continuous epileptic discharges over the RH accompanied by movements of the left arm and leg. Neurological examination revealed increased tone on the left side with decreased power and coordination. Major neurosurgery was contemplated at this stage but the decision was postponed in favour of drug therapy. Over the ensuing 5 yrs, many attempts were made to bring the seizures under control using different regimes of anticonvulsant medications and corticosteroids, but without enduring success.

Preoperatively, H.P. was suffering from frequent seizures, up to six per hour, involving the left arm and leg with deviation of the head to the left. Neurological examination indicated an extensive RH lesion. She had a left homonymous hemianopia, cortical weakness of the left upper limb (grade

3) with no useful movement in the hand and similar weakness of her left leg, and left hemisensory loss with impaired joint position sense. There were increased tendon jerks on the left with a left extensor plantar response and clonus at the left ankle. Preoperative CT scanning had shown increasing right hemiatrophy. EEGs revealed gross abnormality with runs of high voltage sharp-slow wave complexes and no normal background activity.

Psychometry before operation yielded a verbal IQ of 82 and a performance IQ of 67. Verbal memory was mildly impaired and spatial memory skills were severely deficient.

A total right hemispherectomy (Adams' modification) was performed in 1985 and, on the basis of medical history and histopathological features, a diagnosis of 'Rasmussen's encephalitis' was made. Although macroscopic examination revealed a curious absence of focal lesions, detailed histology of the cortex showed varied and extensive degrees of damage and atrophy. In the most severely affected areas, there was narrowing of the full thickness of the cortex with neuronal loss, and astrocytic and vascular proliferation.

Following the operation H.P.'s seizures were totally arrested and she was weaned off anticonvulsant medication within the same year as the operation. She has been attending a local college of further education pursuing courses in English, mathematics and domestic science. After a year's placement in the special needs group, she has now been integrated into the regular stream.

RESULTS

Appendix 1 summarizes background information for both cases and provides a general description of the 2 patients. All the basic language assessments in Appendix 1 reveal poor performance for N.I. and substantially better abilities for H.P. H.P., however, does not perform at the level of a normal 17-yr-old, but more like an 11-yr-old child. This is perhaps not surprising in view of the fact that, over a 5-yr period, she increasingly suffered epileptic seizures (as frequently as six per hour shortly before her operation) which completely disrupted normal life.

Presentation of the results of our detailed testing on the reading performance of N.I. and H.P. will be organized into three main sections: (1) orthography; (2) from orthography to phonology; and (3) from orthography to semantics. Wherever possible, the same tests have been given to the 2 subjects, but in some specific instances this was either not necessary or not feasible. In particular, assessments of some skills (such as letter identification), relevant for N.I., were superfluous for H.P. given her success at more complex tasks that require this subskill; and some of the lists of words that H.P. was asked to read were so far beyond the reading capability of N.I. that their administration would have been unkind to her and uninformative to us.

Orthography

Letter naming, sounding and recognition (N.I. only)

Method. Individual upper case letters were presented in random order and N.I. was asked either to give each letter's name or the sound that it has in a word. Letter recognition was further tested with upper-lower case matching of pairs of letters (n = 24), words (n = 40) and nonwords (n = 40), printed on cards with one item above the other. One member of each pair was in lower case and one in upper case. Half of the pairs in each condition were composed of the same item (e.g., G—g, ROAD—road, FERB—ferb), for which the response should be 'yes', and half were composed of different items (e.g., G—y, ROAD—roar, FERB—ferd), for which the response should be 'no'.

Results. N.I. was very poor at naming randomly presented single letters. She usually performed the task by starting with the letter A and speaking her way through the alphabet, often getting lost and starting again at the beginning. As this strategy made the test very slow to administer, only 17 of the 26 letters were presented. She was correct (i.e., knew where to stop in the alphabet) on 7/17. Her 10 errors consisted of 4 'close' errors of the type that this strategy might be expected to produce (e.g., naming F as 'E' and H as 'J'), 1 other error (P—'H'), and 5 instances where she simply said 'I don't know'. She was worse at sounding than naming letters, producing the sound for S but for no other letter. It is quite clear, however, that these poor performances reflect difficulties in knowing the appropriate sounds, not in recognizing or identifying the letters. In the tests of upper-lower case matching, she was 100% correct with both letters and words, and 95% correct with nonwords.

Number reading

Method. Individual numbers from 1–4 digits in length, written in Arabic numerals, were presented for reading aloud.

Results. N.I. was much more accurate, although no faster, at naming numbers than letters. In fact, she made no errors in number reading; but no number higher than 23 was tested because she used the same serial strategy as with letters, starting at 1 and counting up. In contrast, H.P. was quick and accurate at reading not only 1 and 2-digit numbers but also multidigit numbers, dates, etc.

Word recognition

Method. Recognition of printed words was tested using the lexical decision paradigm, in which subjects are instructed to respond 'yes' if they recognize a letter string as a real word and 'no' if they do not. The first test consisted of 76 high frequency content and function words (all > 350/million, Kučera and Francis, 1967), 3-5 letters in length, plus 76 nonwords created by changing a single letter in each of the test words (e.g., SILCE from SINCE). The second list was derived from a lexical decision test designed by Rickard (1987) to evaluate the influences of word familiarity and word imageability on lexical decision performance. Both of these variables were determined by rating scores on 7-point scales (from the MRC Data Base, Coltheart, 1981); therefore familiarity in this case refers to subjective familiarity rather than objective frequency of word usage as in word frequency norms such as those of Kučera and Francis (1967). The complete test consists of 12 blocks, where three levels of Familiarity (High, Medium and Low) are crossed with four levels of Imageability (High, Medium, Low and Very Low). In view of the restricted educational level of our subjects, we administered only the eight blocks formed from High and Medium Familiarity words at the four levels of Imageability. Examples of these words are shown in Table 1. The nonwords in this test, like those in the first test, were created by changing a single letter in a test word; however the word and nonword members of an orthographic pair (e.g., NERVOUS and NERDOUS) never appeared in the same testing block. The number of real words per block varied between 15 and 30, with a total of 165 words (and an equal number of nonwords) over the eight blocks.

Results. Results for both subjects appear in Table 1. H.P.'s performance on Test 2 showed a significant influence of familiarity, with an average hit rate of 1.0

TABLE 1 LEXICAL DECISION PERFORMANCE*

	N.I.				*H.P*			
	Hit rate	*FP rate*	*d'*	*% correct*	*Hit rate*	*FP rate*	*d'*	*% correct*
Test 1	0.93	0.16	2.46	89%	0.99	0.04	4.07	97%
Test 2	0.88	0.43	1.36	72%	0.90	0.08	2.68	92%

Word sets in Test 2	*(n words)*	*Example*	*Hit rate N.I*	*Hit rate H.P.*
Hi Fam Hi Im	(20)	money	1.0	1.0
Hi Fam Med Im	(20)	brake	0.95	1.0
Hi Fam Lo Im	(30)	proof	0.97	1.0
Hi Fam V Lo Im	(20)	choose	1.0	1.0
Med Fam Hi Im	(20)	knight	0.75	0.95
Med Fam Med Im	(20)	curve	0.70	0.75
Med Fam Lo Im	(20)	eager	0.85	0.75
Med Fam V Lo Im	(15)	vague	0.73	0.67

The words in Test 1 were very high frequency content and function words. Those in Test 2 systematically varied in both Familiarity and Imageability. Hit Rate = the proportion of 'yes' responses to words, FP = False Positive Rate the proportion of 'yes' responses to nonwords, d' = the measure of sensitivity (basically a Z-score) derived from signal detection theory.

* Hi = high, Med = medium, Lo = Low, V Lo = very low, Familiarity (Fam) or Imageability (Im).

on High Familiarity words and of 0.79 on Medium Familiarity words, χ^2 (1 df) $= 21.3$, $P < 0.001$. Obviously no imageability effect was detectable within the High Familiarity words due to ceiling effects. Within Medium Familiarity words, although an unordered χ^2 test was not significant (χ^2, 3 df $= 4.79$, $P = 0.19$), an ordered trend test for the effect of imageability ($\bar{\chi}^2$) just reached significance ($P = 0.04$). Normal adult subjects performing this test (Rickard, 1987) have essentially perfect accuracy on the eight blocks used here; they begin to show small but reliable effects of both variables only in the four Low Familiarity blocks. Therefore, H.P. can be characterized as having a normal pattern of performance on this test; but, due to her restricted reading vocabulary, she shows both overall lower accuracy and 'earlier' sensitivity to the variables of familiarity and imageability than a normal adult. An interaction between frequency and concreteness in lexical decision was also shown to be characteristic of normal adults by James (1975).

In contrast, N.I. achieved reasonable (though never normal) discrimination between words and nonwords only given words of the highest possible frequency, as in the first test. In the second test, like H.P., N.I. showed a significant influence of familiarity: average hit rates on High and Medium Familiarity words were 0.98 and 0.76, respectively; χ^2 (1 df) $= 18.2$, $P < 0.001$. There was no evidence of an imageability effect. Given N.I.'s high acceptance rate on nonwords (FP rate $=$ 0.43), it must be asked whether she showed statistically significant discrimination between Medium Familiarity words and nonwords. A comparison of hit rates on the four Medium Familiarity sets of words to the upper band of the 95% confidence limits on the FP rate (0.49) showed reliable discrimination for the High and Low Imageability sets ($P = 0.016$ and 0.001, respectively) and marginally significant discrimination for the Medium and Very Low Imageability sets ($P = 0.048$ and 0.051, respectively).

From orthography to phonology

Single word reading

Method. For all tests of single word reading, words were printed in lower case letters on individual cards; the patient was given a stack of cards and asked to go through them at her own pace reading each word aloud. Self-corrections were accepted as correct responses; this occurred rarely for H.P. but more often for N.I., at least on words that she had some success in reading (e.g., FRUIT—'juice . . . it's apples and pears and . . . fruit'; RABBIT—'ears and . . . not a hamster . . . a rabbit'). Four different sets of words were used in the assessment of oral reading: (1) (both N.I. and H.P.) 60 content and 60 function words, 3-6 letters in length, all of very high frequency (> 350/million, Kučera and Francis, 1967); (2) (H.P. only: too difficult for N.I.) 40 high and 40 low-imageability words matched for length, frequency and age of acquisition (from V. Coltheart *et al.*, 1988); (3) (H.P. only: too difficult for N.I.) 78 words, 39 with regular and 39 with exceptional correspondences between orthography and phonology (e.g., PINE and PINT, respectively); the two sets are matched for length, frequency and part of speech (from Coltheart *et al.*, 1979); (4) (N.I. only: too easy for H.P.) 235 common concrete nouns selected from the MRC Data Base (Coltheart, 1981), each word with mean values greater than 5.5 for all three of the variables of familiarity, concreteness and imageability; plus 20 common animal names (e.g., COW, TIGER, DONKEY), 10 colour names (e.g., BLUE, YELLOW, PINK) and the number words from ONE to TEN. This total list of 275 words was administered to N.I. over two sessions.

TABLE 2 PERCENTAGE CORRECT ORAL READING

Test no.	*Type of word*	(*n*)	*N.I.*	*H.P.*
1	High frequency content words	(60)	20%	98%
	High frequency function words	(60)	07%	97%
2	High imageability nouns/verbs	(40)	—	88%
	Low imageability nouns/verbs	(40)	—	90%
3	Spelling-to-sound regular nouns	(39)	—	95%
	Spelling-to-sound irregular nouns	(39)	—	79%
4	Common concrete nouns	(235)	35%	—
	Common animal names	(20)	70%	—
	Colour names	(10)	90%	—
	Number words (one to ten)	(10)	100%	—

Results. Performance on all tests of single word reading is shown in Table 2. H.P. read the 120 words in (1) quickly and fluently, making a total of 3 errors: 2 visual errors (QUITE—'quiet' and THOUGH—'through') and 1 error that could be described either as visual or as a regularization of a word with an irregular spelling-to-sound correspondence (GREAT—'greet'). On list (2), normal 10-yr-old children with average reading ability show no effect of imageability (High Imageability words: 84% correct, Low Imageability: 83% correct) whereas age-matched poor readers are sensitive to imageability (54% vs 42%) (V. Coltheart *et al.*, 1988). Table 2 shows that H.P., whose word naming performance is somewhat better than that of an average 10-yr-old reader, is similar in being uninfluenced by imageability. On list (3), H.P. misnamed only 2 of the regular words (CHECK—'cheek'; PROTEIN, a word that she did not know—/prouteni:/) but 8 of the exception words. Every one of these errors is an example of a standard type of children's reading error: sounding a silent letter (for example, SUBTLE—/sʌbtail/), regularizing an irregular correspondence (e.g., SEW—/su:/) or confusing one word with another highly similar in orthography (e.g., THOROUGH—'through'). Consistent with her performance on the standardized reading tests presented in the Appendix, the pattern of H.P.'s oral reading performance is precisely like that of a normal child somewhat younger than her own age of 17 yrs.

N.I.'s attempt to read the words in list (1) reveals a slight advantage for content over function words, but even her performance on the content words was extremely poor. This is probably due to the fact that word concreteness or imageability is a major determinant of her oral reading performance, and these very high frequency content words (e.g., END, PART, PLACE) are mostly rather low in concreteness. N.I.'s performance on this test, together with her performance on the first lexical decision test presented earlier, demonstrates a major dissociation between recognition and oral reading of function words. Her hit rate for recognizing high-frequency function words as real words was 95%, but she was virtually incapable of reading any of these words aloud.

N.I.'s success rate on list (4) is shown in Table 2, and Table 3 presents the results of an error analysis based on the classification scheme typically used in analysing the reading errors of adult deep dyslexic patients (Coltheart *et al.*, 1980). N.I.'s error pattern is strikingly similar to that of acquired deep dyslexic patients,

TABLE 3 DETAILED DESCRIPTION OF N I 'S READING RESPONSES TO COMMON CONCRETE NOUNS (n = 235)

Response Category	*Examples*	*Number*	%
Correct	SHOP THUMB	81	35
Omission	POND RUG	79	34
Circumlocution	HOTEL→ 'It's a flat and . . a room and you stay a couple of days' THIEF→ 'The bank, and lots of money but I can't say it'	26	11
Semantic error	ARM→ finger; PIGEON→ cockatoo	17	7
Morphological error	DUCK→ ducks; SMOKE→ smoking	12	5
Part response	NEWSPAPER→ paper; SAW→ hack-saw	7	3
Visual error	BUSH→ brush; FROST→ forest	7	3
Visual and/or Semantic	MUD→ muck; SWALLOW→ swan	4	2
Other	JERSEY→ diamonds, sapphires	2	—
	Total	235	100

although there are also some differences, quantitative if not qualitative. First, although published cases of adult deep dyslexia show considerable variation in reading skill, a number of them would succeed in reading the majority of words selected to maximize the performance of a patient sensitive to frequency, concreteness and imageability. In comparison, N.I.'s overall success rate was unimpressive, although she was better on the special categories of animals, colours and numbers (the last of which she read, just as with Arabic numerals, by counting up from one). Secondly, whilst there is also substantial variability in proportions of the various error types for different deep dyslexic patients (Shallice and Warrington, 1980), N.I. has a higher rate of omissions and a lower rate of visual errors than most of the reported cases.

Of more note than the differences listed above, however, are the resemblances: in particular, in response to concrete nouns, N.I. produced a number of single word semantic paralexias and circumlocutions, both of which reflect (at least partial) comprehension of a printed word despite failure to retrieve its correct phonology. Single word semantic paralexias have occupied a central role in considerations of deep dyslexia (Coltheart *et al.*, 1980). These errors suggest a patient who, lacking any direct mechanism(s) for translating an orthographic string into a phonological code, is forced to do so entirely with reference to the word's meaning.

Comparison of reading with naming (*N.I. only*)

Whenever poor oral reading is observed in a patient with limited speech output, the hypothesis of a single deficit at the level of phonological output, responsible for both problems, should be considered. One method of assessing this hypothesis is to compare the patient's success at producing a set of names, first in response to pictures typically named by those words and secondly in response to the printed words corresponding to the names. Such comparisons have proved informative with anomic patients who display the characteristics of either surface dyslexia (e.g., Goldblum, 1985; Kremin, 1985; Margolin *et al.*, 1985) or deep dyslexia (Howard, 1985). This issue does not arise for H.P., whose naming and oral reading performance was normal in pattern albeit poorer than average for her age; but it is germane to N.I. Her scores on naming tests and her spontaneous speech indicate substantial anomia; is it possible that many of her failures in oral reading have the same cause, that is, a limit on either the size of or the accessibility of her speech output lexicon? It is already clear that the entirety of her reading impairment cannot be explained in this way, since her spontaneous speech is well supplied with function words, virtually none of which she can read aloud. The production of function words in spontaneous speech may however be supported by other processes (syntactic, prosodic) which do not contribute significantly to single-word oral reading. Therefore, with regard to content words, it is still pertinent to compare N.I.'s naming and reading.

Method. The stimulus materials for naming consisted of 54 line drawings of people engaged in common actions (e.g., a girl climbing a ladder, a boy combing his hair, a man reading a book, etc.). For reading, each of these drawings was converted into a simple written sentence describing the picture, with the verb underlined. The 54 line drawings and their corresponding sentences were divided into two sets, A and B. On one day, set A was given for naming and set B for reading, and on another day, the reverse. N I was asked to produce the verb from both picture and sentence, with the instruction (and given examples) that it was only necessary to say the action word rather than the whole sentence. The main reason for presenting the written verbs in a sentence context was to balance as much as possible the amount of potential information in the two conditions. The picture for the action of climbing shows not only the person climbing but also a ladder, which may facilitate retrieval of 'climbing'. The presence, therefore, of the written word LADDER in the sentence might provide the same assistance with regard to oral reading of CLIMBING.

TABLE 4 COMPARISON OF READING AND NAMING FOR N I
54 COMMON ACTION WORDS

		Naming		
		Correct	*Incorrect*	*Total*
Reading	Correct	15	2	17
	Incorrect	26	11	37
	Total	41	13	54

Results. N.I.'s performance, shown in Table 4, reveals a highly significant advantage for naming over reading ($P < 0.001$ by a two-tailed McNemar test). N.I.'s level of success at naming actions demonstrates that her failure to read the corresponding words cannot be attributed to their absence from or inaccessibility in her speech lexicon. Interestingly, a number of adult deep dyslexic patients who have been assessed on this same comparison (Howard, 1985) show a significant advantage in the opposite direction, that is, better reading than naming.

Nonword reading

Method. Thirty simple nonsense words (such as NEG, LOAT, FOD) were printed on individual cards and presented to both H.P. and N.I for oral reading

Results. H.P.'s performance, shown at the top of Table 5, is certainly normal for her reading age and probably even normal for her chronological age (Masterson,

TABLE 5 PERCENTAGE CORRECT PERFORMANCE ON VARIOUS TESTS OF PHONOLOGICAL PROCESSING

	n	*N I.*	*H.P.*
Nonword reading	30		
Strict criterion		0	80
Lenient criterion		0	97
Nonword repetition	30	100	100
Auditory rhyme judgements	60	93	95
Rhyme production	20	0	100
Phoneme deletion	24	0	96
Phoneme addition	24	0	100

1985). N.I., on the other hand, could not read any of the nonwords. Under conditions of extreme encouragement to say what a particular nonword looked like or what she thought it might sound like, she produced visually similar real words to a few of the items (e.g., NOKE—'coke', FOD—'it's supposed to be a fog'), but her preferred response was always 'I don't know, I'm so sorry'. It should be clear that this is a failure specifically in the ability to translate orthography to phonology: N.I. has no impairment either in recognition of the component letters of a nonword (as demonstrated earlier by her virtually perfect matching of upper and lower case nonwords) or in the ability to produce nonwords orally. Asked to say the same 30 nonwords in an immediate repetition task, she repeated every one perfectly.

Other phonological tasks

It is now thoroughly established that explicit awareness of the phonological structure of words is intimately related to the acquisition of reading skill (*see*, e.g., Liberman *et al.*, 1974; Rozin and Gleitman, 1977; Morais *et al.*, 1979; Bradley and Bryant, 1983). This issue, which has been at the forefront of research on developmental reading disorders (Bertelson and De Gelder, 1988), has been largely ignored in work on acquired disorders. Acquired dyslexic patients are typically tested on nonword reading; but phonological segmentation and assembly, undoubted prerequisites for nonword reading, are rarely assessed (but *see* Derouesné and Beauvois, 1985, for an exception). The fact that deep dyslexic patients like D.E. and P.W. (studied extensively by Patterson, 1978, 1979, and Morton and Patterson, 1980*a*,*b*) are completely incapable of either deleting a phoneme from or adding a phoneme to a spoken word appears not to have been reported in the literature.

Method. Four relevant tasks in the auditory/phonological domain were administered. (1) 60 pairs of monosyllabic words (30 of which rhyme) were spoken to the subject who was instructed to say 'yes' if the 2 words rhymed and 'no' if they did not. (2) The subjects were requested to produce a rhyme for each of 20 single-syllable spoken words. (3) The subjects were instructed to delete the first sound from each of 24 spoken words and say what remained. All stimulus items yielded another real word if the deletion was done properly (e.g., 'mother', 'gold', 'witch', 'meat', 'steam', etc.). (4) H.P. and N.I. were asked to add a sound on to the front of a spoken word and produce the result; as with the phoneme deletion task, correct responses to all 24 items were real words (e.g., /m/ plus 'add'—'mad', /g/ plus 'aim'—'game', /h/ plus 'ill'—'hill', /k/ plus 'lock'—'clock', etc.).

Results. As Table 5 demonstrates, each patient made a few errors on the auditory rhyme judgement test, but in fact they were both reasonably (and equally) good at it. N.I., however, failed totally on all three of the other tasks. In rhyme production, N.I. could only repeat back an example just given to her. Offered 'cat' and 'bat' as a sample rhyme, if she was immediately asked to give a rhyming word for 'cat' she would say 'bat'; but she could never produce either a different rhyme for 'cat' or a rhyme for a test word not used in an example. Asked to provide a rhyming word for 'five' (and note her near-perfect performance at judging that 'five' and 'hive' rhyme whilst 'five' and 'give' do not), she responded 'ten'. With phoneme deletion, even after numerous examples, N.I. had no idea how to perform the task. Despite attempts to facilitate her performance with an easier version of the test in which the first sound of the word was identified for her (e.g., the first sound of 'meat' is 'mmm'; if you take 'mmm' away from 'meat', what is left?), the task remained beyond her ability. Finally, for phoneme addition, N.I. could repeat the 2 individual elements of each stimulus presentation but never succeeded in blending them into a single response word.

Apart from recognition of spoken rhymes, N.I. is utterly lacking in any awareness of or ability to manipulate the phonological structure of spoken words. Given what is known about the relationship of these skills to reading acquisition, N.I. (who apparently learned to read in a perfectly normal manner at a perfectly average age) would almost certainly have been capable of performing these tasks before her illness. This suggests that phonological manipulation is an ability completely lateralized to the LH. H.P.'s success on these tasks is certainly consonant with this view. She made one error in phoneme deletion (asked to delete the first sound of 'stall', she replied 'all') but her performance on these tasks was essentially normal.

From orthography to semantics

Precision of comprehension

Method. Some indication of the basic ability of both N.I. and H.P. to comprehend single printed words is offered by their performance at matching words to pictures (*see* the visual BPVS scores in Appendix 1). This test does not, however, provide an adequate basis for conclusions regarding precision of comprehension. Success in matching the printed word HAND to a picture of a hand where the alternative choices are pictures of a duck, a ball and a shoe can assuredly be achieved on the basis of very gross or even partial comprehension of the word. To obtain a more demanding test of word comprehension, Howard and Orchard-Lisle (1984) developed the Pyramids and Palmtrees test in which 1 of 2 response words (e.g., BUTTERFLY and DRAGONFLY) must be selected to go with a third word (CATERPILLAR). The test was designed such that the 2 response words in any triad are semantically related (usually they are coordinates); a correct choice between them thus requires a reasonably precise understanding of the meaning of the 3 component words composing each item of the test. An additional advantage of the Pyramids and Palmtrees test is that it can be administered with either words or pictures. Performance by N.I. and H.P. on this test using words as stimuli will provide a better indication of their detailed comprehension of written words, and a comparison of this with their scores on the same test using pictures as stimuli will provide some perspective on their semantic knowledge as accessed through these different modalities. The two versions of the test were administered to each patient in different sessions with several months intervening between them.

Results. Performance is shown in Table 6. H.P. made 3 errors with the word version and 2 with the picture version; although these scores are slightly below the means for control groups of normal adult subjects (99%; D. Howard and K. Patterson, unpublished observations), they are just within the normal range as the maximum number of errors made by any control subject was 3. N.I. showed subnormal performance even on the picture version but a significant advantage on pictures over words; χ^2 (1 df) $= 9.01$, $P < 0.01$. By a binomial test, her

TABLE 6. PERCENTAGE CORRECT PERFORMANCE ON TWO COMPREHENSION TESTS*

	n	*N.I.*	*H.P.*
Pyramids and Palmtrees			
Words	50	62	94
Pictures	50	88	96
LUVS			
Printed words	40	85	100
Spoken words	40	98	100

* Chance performance on Pyramids and Palmtrees = 50% and on LUVS = 20%.

performance on the word version is only marginally ($P = 0.06$) above the chance level of 50%.

The nature of comprehension errors

A much discussed issue with regard to deep dyslexic patients (*see*, e.g., Morton and Patterson, 1980*a*; Newcombe and Marshall, 1980; Patterson and Besner, 1984) concerns the locus of their semantic errors in oral reading (e.g., SWAN—'duck'). If such errors reflect only a problem in the procedures whereby semantic features specify a phonological response, then a patient who reads SWAN as 'duck' ought to succeed in selecting a picture of a swan (rejecting the duck) in response to the printed word SWAN. If, on the other hand, the reading error reflects a lack of the precise semantic knowledge that enables a person to know the difference between swans and ducks, then one would expect the patient to make errors in the picture selection task as well. In fact, amongst a set of adult deep dyslexic patients who have been given this sort of test (*see* Bishop and Byng, 1984), some do and some do not make semantic errors in word/picture matching, suggesting two different sources of the reading errors. N.I. makes semantic reading errors; will she also make semantic comprehension errors?

Method. Kay *et al.*, (1989) have designed a word/picture matching test, based on the principle of Bishop's LUVS test (Lexical Understanding with Visual and Semantic Distractors; *see* Bishop and Byng, 1984). Each of the 40 items comprises 1 word such as NAIL (either spoken or printed) and 5 line drawings: the correct item (for this item, obviously, a nail), a visually similar distractor (a pencil), a close semantic distractor (a screw), a distant semantic distractor (a pair of pliers) and an unrelated distractor (a letter: the sort that you post). The two versions of the test (once with printed words and once with spoken words) were administered to both N.I. and H P., in separate sessions with several months intervening

Results. H.P.'s performance was perfect in both modalities. N.I.'s single error in the auditory modality was choosing the unrelated alternative to a target word that she did not know, 'syringe'. Her 6 errors in the visual modality comprised 3 choices of a close semantic distractor, 1 distant semantic alternative, 1 visually similar alternative and 1 unrelated distractor. Even though two-thirds of her errors with printed words involved choice of a semantically related alternative, the small total number of errors clearly prevents statistical support for a claim of semantic errors in this task. It should be noted, however, that claims for semantic errors in word-picture matching both for split-brain patients (patients L.B. and N.G., Zaidel, 1982) and for some deep dyslexic patients (e.g., patients V.S. and R.P., Bishop and Byng, 1984) have been based on total numbers of errors and proportions of semantic errors no greater than those shown by N.I.

DISCUSSION

The Introduction to this paper described two neuropsychological approaches to the question of RH representation of reading skills. In one, with the focus on a patient with primary or sole use of the RH, the basic approach is to examine the extent and nature of reading performance possible. In the other, where a patient with primary or sole use of the LH is studied, the question is whether any reading deficit is found which might be attributable to the absence of a contribution from the RH. It was argued for both approaches that the most convincing source of evidence would be cases of hemispherectomy for neurological disease of late onset. Now that 2 such cases have been presented, what can be concluded about reading with one hemisphere?

N.I., whose symptoms of LH abnormality commenced at the age of 13 yrs and whose LH was removed at the age of 15, is poor at virtually all aspects of reading; but her pattern of reading performance is by no means one of undifferentiated impairment. She is essentially perfect at recognizing letters, although not very successful at naming them and totally unable to give their sound equivalents. She is reasonably good at discriminating very common words from orthographically similar nonwords, but her lexical decision performance falls off quickly as word frequency declines. She can comprehend printed words (as measured by matching to pictures) when these correspond to common concrete objects, but she occasionally makes semantic errors in this task, and her success is dependent upon maximal degrees of both word familiarity and concreteness. She also has some degree of success in oral reading of the most familiar and highly imageable words, but here, too, she is prone to semantic paralexic errors. That she only succeeds in oral reading with words of the type that she can understand is no coincidence: instead, it reflects the fact that she has no means of translating a printed word into a phonological response except on the basis of its meaning. She cannot read aloud nonsense words at all (although she repeats them perfectly). She cannot pronounce subcomponents of written words and, indeed, within the domain of the spoken word, she has no awareness that words are divisible into subcomponents.

Before further discussion of N.I.'s reading, it is necessary to consider the justification for generalizing from her reading performance to the representation of reading abilities in the RH of right-handed adults, either those who are neurologically normal or those who were neurologically normal prior to a stroke or other incident. The potential obstacle to such generalization is N.I.'s speech. Although she is very aphasic, her speech is rather better than and quite different from the speech of globally aphasic stroke cases with massive LH lesions, most of whom are either severely agrammatic, or restricted to single word utterances, or even restricted to the same recurring utterance. N.I.'s relatively good speech raises two questions. (1) Might she have had either RH or bilateral representation of language before the onset of her brain disease? (2) If the answer to the first question is negative, with the consequent interpretation that her limited speech represents interhemispheric reorganization of speech in response to the onset of her brain disease, then might the same be true of her limited reading ability?

Most easily rejected is the notion that N.I. might originally have had RH dominance for language: the fact that all her language abilities are now so impoverished would be inexplicable. Almost as easy to reject, on statistical grounds, is the notion that N.I. had bilateral representation of speech. In a sample of 140 right handers given sodium amytal tests (Milner, 1975), the procedure indicated LH speech representation for 134 individuals (96% of the sample) and RH speech representation for 6 (4%). Not a single case had bilateral speech. Amytal testing is necessarily time limited and therefore inadequate for assessing a range of language functions. Nevertheless, the most likely conclusion is that N.I., completely right handed and completely normal until age 13, had normal LH dominance for language.

Resolution of the remaining query is less straightforward. In the first instance, the conclusion that N.I.'s speech represents a late reorganization of hemisphere dominance could be surprising in the light of prevalent assumptions about complete lateralization of language by about the age of 5 yrs (*see* Searleman, 1977, Zaidel, 1979, and Hahn, 1987, for discussion). However, there has also been an alternative view that some degree of plasticity remains until puberty (Basser, 1962; Lenneberg, 1967) or even into adulthood (Teuber, 1975). Furthermore, an extensive review of the hemispherectomy literature by St James-Roberts (1981) revealed considerable variability of language function in left hemispherectomy cases independent of age at onset. Finally, it must be remembered that N.I. is severely impaired in every aspect of language. The debate as to whether left hemispherectomy can fully spare certain aspects of language processing only arises for cases with early onset of disease (e.g., Dennis and Whitaker, 1976; Dennis, 1980; Bishop, 1983; Strauss and Verity, 1983).

If N.I.'s speech reflects hemisphere reorganization, then presumably no one would attempt to generalize from her spoken language to the probable representation of speech abilities in the RH of a right-handed adult who is either normal or has just suffered a stroke. Why is it then legitimate to draw inferences about probable RH reading abilities in such individuals on the basis of N.I.'s reading performance? Relevant arguments offer plausibility but no proof. The first point concerns the ecological importance to an individual of basic speech comprehension and production, without which he or she must live in genuine isolation. The same cannot be said of reading skills. In response to a deteriorating dominant hemisphere, therefore, it seems plausible that the brain will concentrate on reestablishing as much basic communication skill as possible in the other hemisphere. The second point is that, from the onset of N.I.'s illness to the present, and including the time at which brain reorganization was presumably occurring, N.I. had constant exposure to and experience of comprehending and producing speech but virtually no reading experience. The final point is that her reading skill is dramatically inferior to her speech comprehension and production. In assessments pertaining to the present study, she comprehended many spoken sentences but no written ones; she repeated sentences up to about 5 words in length without error but never correctly read aloud a sentence; she easily repeated spoken nonsense words but failed entirely to read them aloud. If N.I.'s RH did take over reading skill as a result of reorganization, it did so rather unsuccessfully. The most plausible assumption is that N.I.'s current reading abilities are essentially like (and in particular no better than) those of the RH of a normal right-handed 13-yr-old girl.

If this interpretation is accepted, then the data for N.I. probably constitute the best available source of evidence on the reading capacities of the nondominant hemisphere. These data can now be compared with evidence from other sources regarding this question.

N.I.'s reading performance is highly similar to the pattern demonstrated by Zaidel and his colleagues (e.g., Zaidel and Peters, 1981; Zaidel, 1982) for the split-brain patients L.B. and N.G. in reading tasks with stimuli lateralized to the left visual field. The major difference is that N.I. (with her limited speech represented in the RH) can accomplish some oral reading whereas L.B. and N.G. (with their normal speech represented in the LH) cannot read aloud words presented in the left visual field. The main similarities are an inability to convert orthography to phonology by any direct translation procedures, sensitivity to the familiarity and especially to the concreteness or imageability of words, and the occurrence of at least some semantic errors in matching printed words to pictures. Many writers have expressed worries about generalizing from split-brain patients to normal subjects (e.g., Lambert, 1982; Gazzaniga, 1983; Patterson and Besner, 1984; Coltheart, 1985). Furthermore, there is extensive debate regarding interpretation of the RH language skills shown by L.B. and N.G., not only with regard to normal subjects but also in relation to other split-brain cases (Gazzaniga, 1983; Levy, 1983; Zaidel, 1983; Myers, 1984). Although such generalizations are inherently risky, some of the results are impressively consistent. In particular, Zaidel's results for L.B. and N.G. and the present results for N.I. suggest the same conclusions about the nondominant RH's capacity for reading.

Secondly, N.I.'s reading performance is identical in pattern, though not in level, to most cases of acquired deep dyslexia described in the literature. As indicated in the Introduction, a strong case for the equation of deep dyslexic reading with RH reading has been made by Coltheart (1980, 1983) and Saffran *et al.* (1980), and supported by Landis *et al.* (1983), Zaidel and Schweiger (1984), Jones and Martin (1985) and others. One of the authors of this paper has been associated with grave reservations regarding this notion (Patterson and Besner, 1984; Marshall and Patterson, 1985), but it is clear that the hypothesis receives a considerable boost from the current results on N.I.'s reading. The case is not (because it cannot be) proven. First of all, there is the important point made by Rabinowicz and Moscovitch (1984) that some types of LH damage may result in residual LH language abilities resembling the abilities of the isolated RH. Thus acquired deep dyslexic reading performance could still be LH reading, at least in some patients. Furthermore, the quantitative differences between N.I.'s reading skill and that of most deep dyslexic patients should not be ignored; some possible accounts of this discrepancy are mentioned below. Despite these reservations and some unresolved issues (such as alexia without agraphia: *see* discussions by Landis *et al.*, 1980; Patterson and Besner, 1984; Zaidel and Schweiger, 1984; Shallice and Saffran, 1986), the empirical conclusion is clear: adult deep dyslexics, who may be reading with the RH, and N.I., who must be reading with the RH, are strikingly similar.

There would seem to be three potential explanations for N.I.'s quantitatively poor performance (e.g., in oral reading of familiar concrete words) relative to many published cases of acquired deep dyslexia resulting from cerebrovascular lesions, head injury or missile wounds. The first possibility relates to the fact, noted earlier, that N.I.'s reading experience came to a virtually complete halt at the age of 13. If a normal LH-dominant individual has a RH reading lexicon, and if learning within already established subcomponents of a skill continues throughout an individual's life, then perhaps the reading lexicon in N.I.'s RH would be expected to underestimate the RH reading lexicon of a 50-yr-old (a more typical age for onset of acquired deep dyslexia). It may be worth noting that one of the few relatively young cases of acquired deep dyslexia, W.S. (Saffran, 1980), apparently had extensive reading instruction after his missile wound at the age of 11 yrs (*see* Saffran *et al.*, 1980). This is not, however, true of the deep dyslexic patient D.E. (Patterson, 1978, 1979) with a brain injury at the age of 16 yrs, who had left school at 15 and was probably no great reading enthusiast at any age. While by no means the best reader of the various well-studied cases of acquired deep dyslexia, D.E.'s performance is substantially better than N.I.'s.

The second possibility concerns the neurological and cognitive status of N.I.'s RH: while this evinces no gross damage, it did suffer the effects of extremely severe LH seizures over a period of about 2½ yrs. The majority of adult deep dyslexic patients sustained an abrupt insult (such as a cerebrovascular lesion), confined to the LH. Perhaps their RHs are more intact than N.I.'s RH, and that explains their superior reading. To the extent that this argument has force, then the RH reading performance of split-brain patients (with a history of seizures) may constitute a more satisfactory basis for comparison with N.I. And indeed, as emphasized by Patterson and Besner (1984), the split-brain cases extensively tested on RH reading (*see* references by Zaidel) are, like N.I., qualitatively similar but quantitatively quite inferior to deep dyslexic patients.

Both of the first two explanations are predicated on the assumption that deep dyslexic reading arises primarily or exclusively from the RH. The remaining explanation acknowledges that, however damaged it may be, these patients do have a LH whereas N.I. does not. The evidence may converge convincingly on a major RH *contribution* to the pattern of performance in deep dyslexic reading; but it remains possible that most deep dyslexic patients read at a higher level than N.I. because their reading can rely both on an intact RH and some limited LH resources.

Turning much more briefly to H.P. and the other approach to the question of RH reading, the present assessment indicates that H.P.'s reading abilities are delayed but in no way deviant. Her reading lexicon is smaller than that of a normal 17-yr-old, and thus she is naturally more sensitive to variables such as familiarity and spelling-to-sound regularity. These are, however, quantitative differences only; there were no qualitatively abnormal features in H.P.'s reading, nor was there any subskill of a normal person's reading profile that was lacking in H.P.'s abilities. The discrepancy between her chronological and reading ages may be entirely explicable in terms of the 5 yr history of preoperative illness. H.P.'s performance suggests that the RH plays no necessary role in supporting reading skills, at least of the type assessed in this study (mainly single word recognition, comprehension and pronunciation).

Zaidel and Schweiger addressed themselves to the question of the role of the RH in normal reading: 'Perhaps it is important both for reading acquisition and for mature, efficient reading. In particular, the RH may be important for quick pattern recognition during speed reading, and for semantic-thematic orientation to a situation or narrative. On this account, loss of RH contribution in adults would lead to subtle deficits in higher-order reading which are rarely assessed in the neurological clinic and have yet to be formally tested in split-brain patients.' (Zaidel and Schweiger, 1984, p. 362).

These three points all seem thoroughly sound. Normal acquisition of any skill as complex as reading undoubtedly requires two functioning hemispheres, and there is indeed evidence that children with one hemisphere have difficulty learning to read whether it is the LH or the RH that has been removed. Although rather little is known on the subject of speed reading, there is an intriguing report by Andreewsky *et al.* (1980) of speed-reading ability in a case of deep dyslexia. Finally, although assessments of possible higher order language or reading deficits in patients with RH lesions are rare, a few are beginning to appear (e.g., Cavalli *et al.*, 1981; Wapner *et al.*, 1981; Chiarello and Church, 1986; Grossman and Haberman, 1987). Most of these studies have revealed significant (if sometimes small) deficits, relative to control subjects, in patients with RH lesions, especially (e.g., in the Grossman and Haberman study) for anterior RH lesions. There is, however, no indication that such deficits are specifically concerned with linguistic abilities as opposed to more general higher order cognitive skills.

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APPENDIX

The table below provides general background information and standardized test results for the 2 patients. The first three sections of the table are self-explanatory, but the individual background tests on language abilities may require brief description.

1. The picture naming test from Oldfield and Wingfield (1965) consists of 36 line drawings of objects.

2. The Token Test (De Renzi and Vignolo, 1962) assesses auditory language comprehension by asking the subject to arrange tokens of various colours, shapes and sizes in response to spoken sentences.

3. TROG (Test for the Reception of Grammar, Bishop, 1982) also measures sentence comprehension. The subject is asked to point to 1 of 4 pictures to match a spoken sentence. Each of the 20 blocks in this test assesses a different aspect of syntactic comprehension, and 'passing' a block requires correct picture matching on all 4 items within the block.

4. The British Picture Vocabulary Scale (Dunn and Dunn, 1982) measures comprehension of single words, again with four alternative forced choice picture matching. The test, consisting of 150 items, is stopped when the subject reaches ceiling (6 errors in 8 consecutive items), and the subject's score is calculated by subtracting the total number of errors from ceiling. Since items occur in graded order of difficulty, the item number at which the subject makes his or her first error is also informative.

5. Schonell (1942) constructed standardized tests of (a) reading single words aloud and (b) writing single words to dictation, yielding estimates of reading and spelling age.

6. The Neale test of text reading (Neale, 1966) provides reading-age estimates for the speed and accuracy of oral reading and also for reading comprehension based on questions about the content of the text that has just been read.

Background information

	N.I.	H.P.
General		
Hemisphere removed	L	R
Original handedness	R	R
Year of birth	1969	1970
Age at onset of symptoms (yrs)	13	10
Age at operation (yrs)	15	15
Age at testing (yrs)	17	17
Postoperative IQ (NI: WISC-R; HP WAIS)		
Verbal IQ	55	80
Performance IQ	80	75
Full scale IQ	66	77

Wechsler Memory Scale	N.I.	H.P.
MQ (based on adjusted age correction)	(62)	(83)
Logical memory—immediate	29%	49%
Visual reproduction—immediate	61%	39%
Digit span—forwards	4	4
—backwards	3	2
Language tests		
Naming (Oldfield-Wingfield, n = 36)	39%	92%
Token Test (n = 62)	69%	95%
TROG		
Blocks passed (of 20)	12	18
Total errors (of 80)	20	3
BPVS with spoken words		
Raw score	71	108
Item number of first error	34	58
BPVS with written words		
Raw score	43	93
Item number of first error	16	62
Schonell oral reading		
Number of words read	10	69
Reading age equivalent	6:9	11:1
Schonell spelling		
Number of words written	3	57
Spelling age equivalent	5:4	10:8
Neale reading age equivalents for:		
Rate	< 6:6	9:1
Accuracy	< 6:0	10:10
Comprehension	< 6:3	11:4

Brain (1989), **112**, 65–83

DISTAL MYOPATHY WITH RIMMED VACUOLE FORMATION

A FOLLOW-UP STUDY

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SUMMARY

A long-term follow-up study of patients with familial distal myopathy with rimmed vacuole formation and a review of the literature indicates that the prognosis of the disorder was extremely poor as to daily life Although the initial symptom appearing in early adulthood was muscular wasting and weakness in the legs, especially the distal muscles, severe generalized skeletal muscle involvement with sparing of the facial, extraocular, bulbar, intercostal and diaphragm muscles was recognized in the advanced stage. The disease is probably inherited as an autosomal recessive trait, while there is a considerable female preponderance, the female-to-male ratio being 2 : 1. The disorder is distinguishable from various types of distal myopathy on the basis of clinical and pathological findings, and other myopathies with rimmed vacuole formation, including inclusion body myositis, from a prognostic viewpoint

INTRODUCTION

We previously described 3 patients in 2 families with distal myopathy with rimmed vacuole formation (DMRV) in which the main muscle pathology was rimmed vacuole formation with no apparent muscle fibre necrosis (Nonaka *et al.*, 1981, 1985). In these patients the muscle weakness seemed to progress rather rapidly, but the prognosis of DMRV remained uncertain.

Although the rimmed vacuole formation and intranuclear filamentous inclusions seen in DMRV are also characteristic findings in inclusion body myositis (IBM), a means of differential diagnosis of the two disorders has not been fully established. In this paper, therefore, we describe 3 patients who were followed for 7 yrs, and 2 additional patients in another family. In addition, we review well-described patients with DMRV in Japan and discuss the nosological status of this disorder.

CLINICAL OBSERVATIONS

(The pedigrees of the 3 families are shown in fig. 1. The parents of Cases 1 and 2 were first cousins. Family members III-7, III-19, IV-2 and IV-3 in Family K,

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II-5, II-17 and III-1 in Family S, and II-5 in Family Y were examined clinically. The serum creatine kinase (CK) levels in members III-7, III-19, IV-1, IV-2 and IV-3 in Family K, and II-5, II-17 and III-1 in Family S were within normal limits.

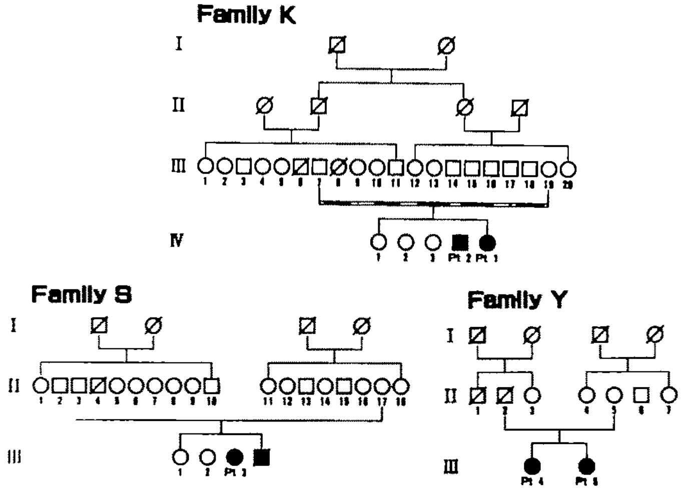

FIG. 1 Pedigrees of the three families. Closed symbols = affected.

Family K

Case 1 (sister of Case 2)

A 33-yr-old housewife developed gait disturbance at the age of 22 yrs. Within a yr she became unable to stand on her toes or to raise her legs above a height of 30 cm. She was admitted to hospital where she received prednisone for 2 months without benefit. When aged 23 yrs, she could not rise from the sitting position without help. A year later her finger muscles became weak, particularly on the left. At the age of 24 she could no longer climb stairs, and 1 year later became unable to descend stairs. At this time she was able to walk only about 30 m on flat ground with the aid of a cane. The findings on physical, laboratory and pathological examination on the first admission have already been reported (Nonaka *et al.*, 1981, Case 1). The fibres with rimmed vacuoles comprised 17.6% in the vastus medialis muscle. A few months after discharge she could no longer stand unassisted and was confined to a wheelchair; she could not propel it by herself because of hand muscle weakness.

She got about on her knees in the house. At the age of 27 yrs she noticed difficulty in raising her arms and lifting up her head in the supine position. By the age of 28 she was unable to wring a towel. She could not use a clothes peg 2 yrs later. At the age of 31, by which time she had to cook leaning against a table, she suddenly fell and suffered severe burns on the face from boiling oil. Thereafter she was unable to stand and moved slowly as shown in fig. 2B. She could not raise her arms above her shoulders, sit up from the supine position or turn over in bed. She sustained frequent injuries to the face because she was unable to save herself with her arms when she fell.

Physical examination was normal except for severe keloid burns and traumatic scars on the face. The cranial nerves were intact apart from moderate wasting and weakness of the sternomastoid muscles bilaterally. The neck and the distal limb muscles were markedly wasted. The proximal muscles were also atrophic, especially in the legs. The neck flexors and extensors were severely weak (MRC Scale 2/5) and there was moderate weakness of the shoulder girdle, arm and hand muscles,

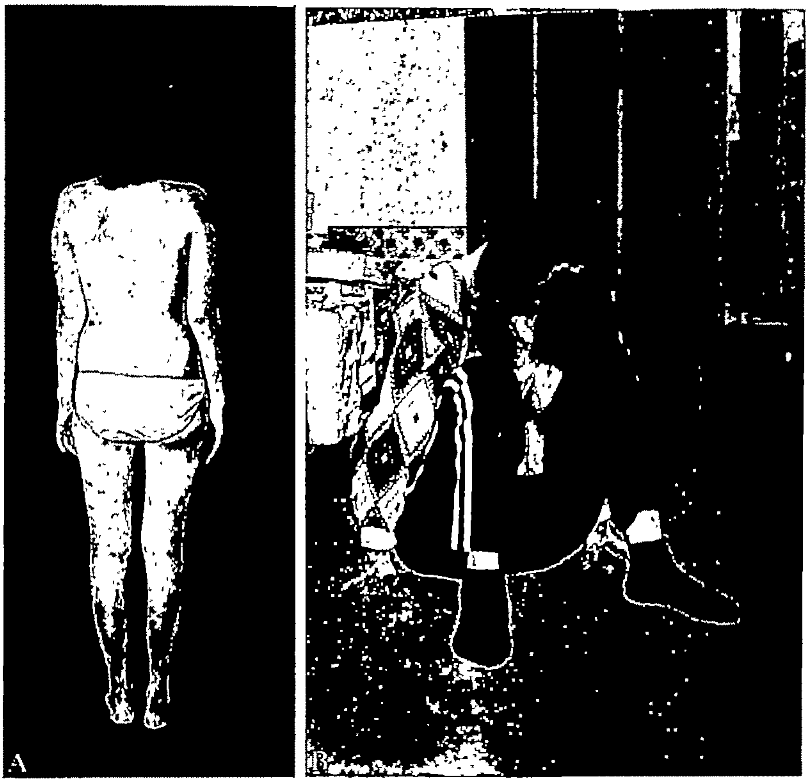

FIG 2 A, photograph of *Case 1* on first admission B, method of locomotion of *Case 1*, 7 yrs after first admission

especially biceps brachii (3/5). The grip was extremely poor bilaterally. Severe muscle weakness was present in the legs (0–1/5), both proximal and distal muscles being equally involved, and the muscles of the trunk also showed marked weakness. The tendon reflexes were all diminished. Neurological examination was otherwise normal.

Case 2 (*brother of Case 1*)

The patient, a 34-yr-old carpenter, was healthy until aged 24, when he experienced progressive difficulty in running and climbing stairs. Two years later he was unable to stand on his toes, and at the age of 27 he could not stand on his heels Physical, laboratory and pathological findings on the first admission have already been reported (Nonaka *et al.*, 1981). Rimmed vacuoles were recognized in 9.2% of fibres in tibialis anterior and none in vastus medialis. After discharge, muscle weakness and wasting of the neck, legs and arms progressed gradually and severe wasting became evident in the neck, biceps femoris and lower leg muscles. The quadriceps femoris muscles appeared somewhat hypertrophied. The neck flexor muscles were markedly weak (2/5) and biceps and triceps brachii were mildly affected (4/5), especially on the right. The finger muscles showed only slight weakness (4/5). There was moderate weakness in the iliopsoas muscles (2–3/5). The quadriceps femoris muscles were of normal strength whereas the thigh abductor muscles showed mild weakness (4/5), and weakness was increasingly severe in gastrocnemius, soleus and the toe flexors (3/5), biceps femoris, tibialis anterior and the toe extensors (2/5) and the hip adductor muscles (1/5). The biceps, triceps and ankle jerks were diminished but the brachioradialis and knee reflexes were normally active. He had a slow, waddling and steppage gait with lordosis He stood up using

Gowers' manoeuvre with marked difficulty. The remainder of the neurological examination was normal.

Family S

Case 3

The patient, a 35-yr-old housewife, became aware of muscle weakness of the lower legs at the age of 20, followed by progressive muscle wasting and weakness of the limb, neck and trunk muscles. Physical, laboratory and pathological findings on the first admission at age 27 yrs have already been reported (Nonaka *et al.*, 1981, Case 3). The fibres with rimmed vacuoles comprised 24.8% in the biceps brachii muscle. When aged 35 yrs, she moved in a squatting position with considerable difficulty, as seen in Case 1. There were scars on her face from frequent falls. The sternocleidomastoid and trapezius muscles were markedly atrophic with moderate weakness (4-/5). Prominent muscle wasting was noted in the neck and lower limbs, and moderate atrophy in the arms. The strength of the neck flexors was 2/5, neck extensors 3/5, deltoid, pectoralis major and biceps brachii muscles 2/5, and triceps brachii, wrist extensors, wrist flexors and finger muscles 4-/5. Grip strength could not be detected with a dynanometer. There was severe weakness (0-1/5) in the iliopsoas, pelvic girdle and all leg muscles. The muscles of the trunk were also markedly weak. She could not turn over from the supine to the prone position or sit up from the supine position. She had equinus feet due to shortening of the calf muscles. The tendon reflexes were all absent. Neurological examination was otherwise normal.

The patient's brother had had progressive muscle wasting and weakness of the lower legs from the age of 20 yrs, similar to that seen in the patient herself. He died in a car accident at the age of 21.

Family Y

Case 4 (sister of Case 5)

A 37-yr-old woman, a kindergarten teacher, had frequent falls at the age of 24 yrs without being aware of limb weakness. One month after an uneventful pregnancy and delivery she became unable to run or to dorsiflex her toes. She also had difficulty in lifting her legs. Within a few months she was unable to flex her knee joints in the supine position. She was seen at a hospital where a diagnosis of polymyositis was made. Myopathic changes were seen in a biopsy of the vastus lateralis. She was placed on 30 mg of prednisone for 6 months without effect. When 28 yrs old she could not climb stairs without support and showed drop feet. At this time she could not raise her head in the supine position and also had proximal weakness in the upper limbs. The weakness of the legs and arms continued to become worse and at the age of 35 she could no longer raise her arms or stand up from a sitting position. She also became aware of weakness of the hands and fingers. A second biopsy from the left deltoid muscle showed myopathic changes with rimmed vacuole formation. At the age of 36 she could not turn over in the supine position. Recently, she became unable to remain standing for more than 5 min, even with support. Physical examination was unremarkable except for some scars on the face and limbs. Severe muscle weakness (3/5) and wasting were observed in the sternomastoid muscles. There was marked wasting in the deltoid and leg muscles bilaterally, apart from the quadriceps femoris muscles which were moderately hypertrophied (a CT scan of these muscles showed a normal density with an increase in volume), and mild wasting in the arms. The strength of the neck flexors was 2/5, and that of the neck extensors and flexors of the interphalangeal finger joints, and the deltoid muscles, 2-3/5, and there was mild weakness (4/5) in the shoulder girdle, biceps brachii, triceps brachii, brachioradialis, and wrist flexor and extensor muscles, especially on the left. Grasping power was mildly decreased (left 6 kg, right 10 kg). The strength of the iliopsoas, biceps femoris, thigh adductor, tibialis anterior and toe extensor muscles was 1/5, and that of the gastrocnemius and soleus muscles, 3/5. The toe flexors were mildly weak (4/5), the quadriceps femoris muscles being of normal strength. The biceps, triceps and ankle jerks were absent, and the brachioradialis and knee reflexes were normally active. She could walk on a flat surface with a prominent waddling and steppage gait with the aid of a cane She was unable to stand or sit up unaided. Examination was otherwise normal.

The serum CK was 75 U/l (normal: 12-75), aldolase, 5 7 IU/l (normal: 1.9-5.2), and myoglobin, 110 ng/ml (normal: < 35). EMG revealed myopathic changes with mild neuropathic changes, such as positive sharp waves and fibrillation potentials at rest. Motor nerve conduction velocity of the right median and tibial nerves was 61 and 47 $m \cdot s^{-1}$, respectively, and sensory nerve conduction velocity in the right median and sural nerves was 65 and 44 $m \cdot s^{-1}$, respectively. At the age of 37, a muscle biopsy was obtained from the left biceps brachii which was mildly weak, and from the left quadriceps femoris which was of normal strength. The former muscle (fig. 3A) contained a number of fibres with rimmed vacuoles (10 4%) and there was a considerable variation in fibre diameter. The vacuoles were rimmed by basophilic granular material on haematoxylin-eosin staining and purple-red material with the modified Gomori trichrome stain. Small vacuoles were occasionally strongly positive for acid phosphatase, whereas in the larger, enzyme activity was increased only at the periphery. Scattered or small groups of angular fibres showed high activity on staining for nonspecific esterase. Neither fibre necrosis nor inflammatory cellular infiltration was seen. Pyknotic nuclear clumps were present. On ATPase staining, the most striking finding was an increased proportion of type 1 fibres (up to about 80%). Type 2B fibres were deficient. Regenerating fibres were not present. The quadriceps muscle (fig. 3B) had an almost normal appearance except for a slightly increased variability in fibre size, with some hypertrophic and a few small angular fibres, and occasional fibres with internal nuclei. There were no fibres with rimmed vacuoles in any of the sections. An electron microscopic examination showed numerous myeloid bodies of various sizes and autophagic vacuoles containing glycogen particles and cytoplasmic debris. The myofibrils were disorganized focally with Z-band streaming. Phagocytes in and around fibres were not recognized. There were no necrotic fibres. No intranuclear or intracytoplasmic filamentous inclusions were seen in either the biceps brachii or the quadriceps femoris biopsy specimens.

Case 5 (*sister of Case 4*)

A 32-yr-old housewife began to have difficulty in climbing stairs when aged 30 yrs. Subsequently, gait abnormality was noticed by her neighbours. At the same time she became aware of an inability to raise her head in the supine position. There was mild muscle atrophy in the distal parts of the legs and marked wasting of the neck muscles. The neck flexors showed severe weakness (2/5). There was mild weakness (4/5) in the sternomastoid, deltoid, periscapular and pectoralis major muscles, especially on the left. The iliopsoas muscles showed marked weakness (left 2/5, right 3/5). The biceps and quadriceps femoris, tibialis anterior, thigh abductor, thigh adductor and toe extensor muscles were mildly weak, especially on the left (4/5). The tendon reflexes were all present but were slightly less active on the left. She showed a mild waddling and steppage gait. Gowers' sign was positive. The remainder of the neurological examination and general physical examination were normal. The serum CK was 189-235 U/l, aldolase, 5.1-7.5 IU/l, and myoglobin, 130 ng/ml. EMG showed myopathic changes with mild neuropathic changes such as positive sharp waves and fibrillation potentials at rest. Motor nerve conduction velocity in the right median and tibial nerves was 68 and 44 $m \cdot s^{-1}$, respectively, and sensory nerve conduction velocity in the right median and sural nerves 68 and 40 $m \cdot s^{-1}$, respectively. A left biceps brachii muscle biopsy revealed moderate variation in fibre size, diameters ranging from 20 to 40 μm. There were many small angulated fibres with rimmed vacuole formation (4.2%). The histochemical characteristics of the rimmed vacuoles were similar to those seen in Cases 1-4. The vacuoles occasionally had high acid phosphatase activity. No inflammatory cell infiltrates or necrotic fibres with phagocytosis were seen. On ATPase staining, there was a slight predominance (59%) of type 1 fibres with mild type 1 fibre atrophy. The ratios of type 2A, 2B and 2C fibres were 24%, 15% and 2%, respectively. There was no fibre type grouping.

On electron microscopic examination, many vacuoles and myeloid bodies were observed in scattered fibres in which myofibrills were focally disorganized. There were numerous small vacuoles

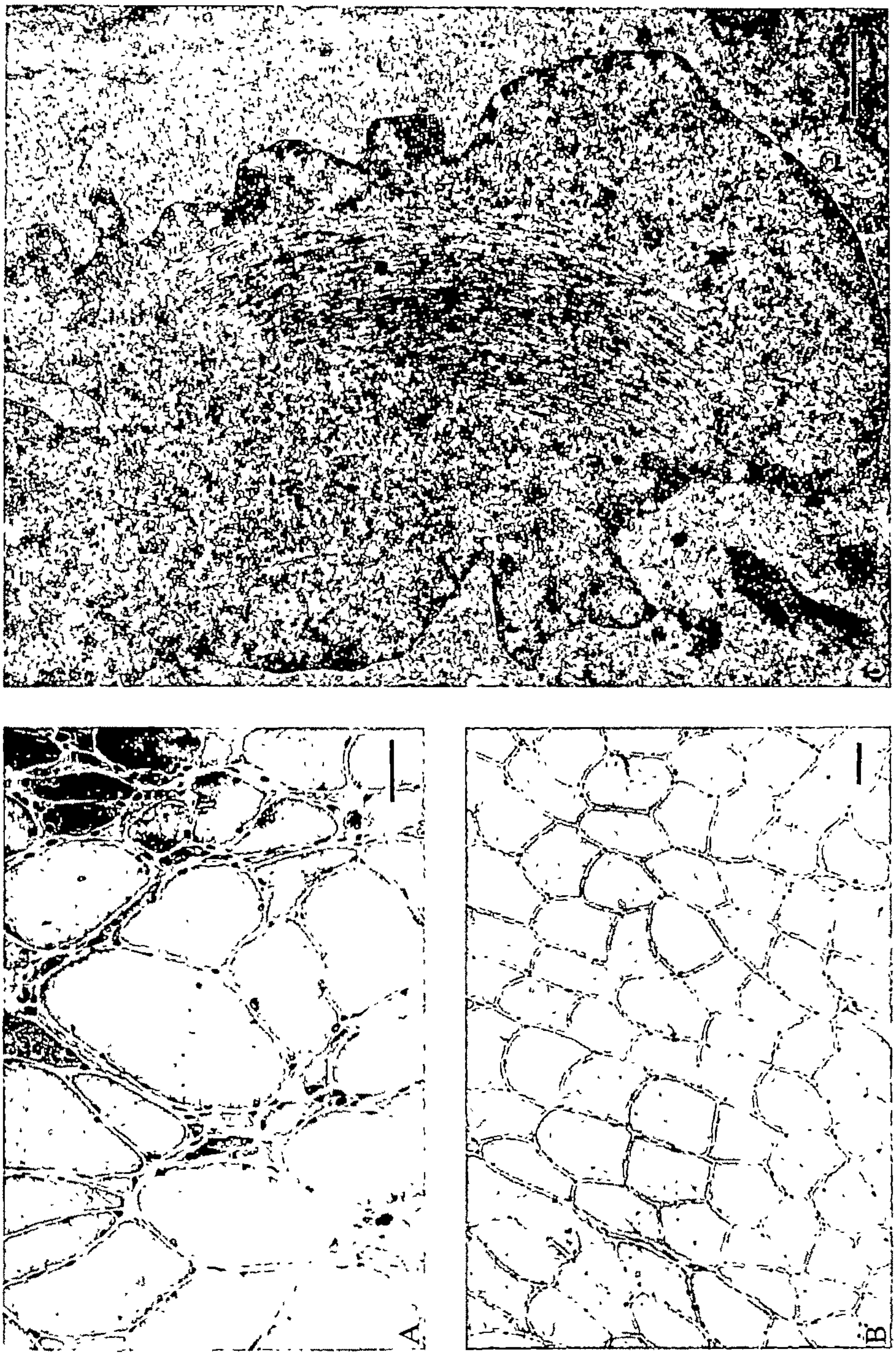

FIG. 3. Pathology of biopsied muscle. A, numerous fibres with rimmed vacuoles in the biceps brachii muscle of *Case 4*. Haematoxylin and eosin Bar = 50 μm. B, almost normal appearance of the quadriceps femoris muscle of *Case 4*. Haematoxylin and eosin. Bar = 50 μm. C, intranuclear filaments in biceps brachii muscle of *Case 3*. Bar = 1 μm.

containing cytoplasmic debris and glycogen particles. No phagocytes were present in or around the degenerative fibres There were no intranuclear or intracytoplasmic filamentous inclusions in the samples examined.

Summary of the clinical observations

The initial symptom of muscle weakness of the legs appeared in the second or third decade in all patients. In the initial stages, distal muscles of the legs were more prominently affected than proximal muscles, while the latter, particularly the iliopsoas and biceps femoris muscles, became involved from an early stage. Drop feet and Gowers' sign became recognizable 1 to 4 yrs after the onset, when the patients had a steppage and waddling gait, and had difficulty in climbing stairs without support. During the period of 2 to 7 yrs from onset the patients became unable to raise the head in the supine position, and at the same time they noticed weakness of the fingers and hands or difficulty in raising their arms. Ten to 13 yrs after onset the patients could no longer stand up by themselves, and had to move around on their knees. Weakness of the proximal muscles of the arms became worse than that of the distal muscles and patients had great difficulty in raising their arms. By 15 yrs after onset the patients showed severe generalized wasting and weakness of muscles except for the facial, extraocular, bulbar and intercostal muscles, and the diaphragm. The patients could not turn over or sit up from the supine position because of severe weakness of the trunk muscles. All noticed that their muscle weakness continued gradually to progress and to become more widespread. The patients complained that their hands and feet felt cold, particularly in the winter, but there was no other sensory disturbance. The patients never had dysphagia, dysarthria, or dyspnoea, nor bladder or bowel dysfunction.

The clinical course, according to the MRC scale, is shown in fig. 4. In the early stages, the tibialis anterior and biceps femoris muscles were much more affected than the gastrocnemius and quadriceps femoris muscles. The neck flexor and iliopsoas muscles were also impaired in the early stages. As the disorder progressed, the entire musculature of the legs and hips became weak, although the quadriceps was spared in 2 cases. In the advanced stages, weakness of both distal and proximal muscles of the upper limbs became apparent, predominantly in the proximal muscles. Ten to 15 yrs after onset, diffuse severe muscle weakness was detected in the legs and hips. On palpation marked wasting of both proximal and distal muscles was found. The consistency of the atrophied muscles was extremely soft even in patients with a long duration of illness. There was no myotonia, muscle tenderness, fasciculation or pseudohypertrophy. Skin rashes, Raynaud's phenomenon or other manifestations seen in connective tissue disorders were not present.

LITERATURE REVIEW (JAPANESE CASES)

A number of patients similar to ours have been reported in Japan: 37 patients including our own were available for the present review (Miyoshi *et al.*, 1970;

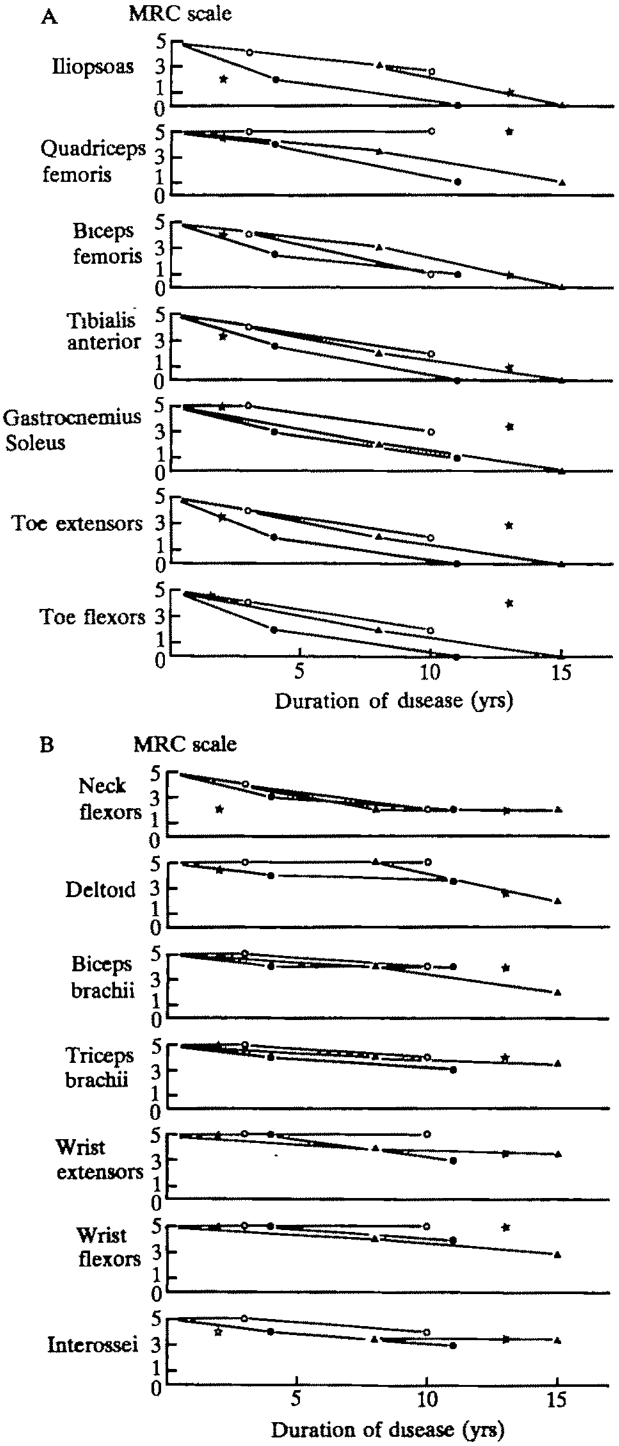

FIG 4. Clinical courses, with muscle weakness expressed on the MRC scale. Closed circles (*Case 1*); open circles (*Case 2*), triangles (*Case 3*), closed stars (*Case 4*); open stars (*Case 5*)

Mizusawa *et al.*, 1980, 1986; Nakanishi *et al.*, 1980; Inoue *et al.*, 1981; Nishitani *et al.*, 1981; Nonaka *et al.*, 1981; Kira *et al.*, 1982; Kumamoto *et al.*, 1982; Matsubara and Tanabe, 1982; Nakanishi and Kuzuhara, 1982, 1983; Tashiro *et al.*, 1982; Tsukagoshi *et al.*, 1984). Clinical details for 37 cases are shown in Table 1. The patients reported by Miyoshi *et al.* (1970), Nakanishi *et al.* (1980), Nakanishi and Kuzuhara (1982) were described in detail again by Kira *et al.* (1982) and Nakanishi and Kuzuhara (1983). The most striking finding of the muscle pathology in all reviewed patients was the presence of a number of fibres with rimmed vacuoles, but with no evidence of 'myositis' as evidenced by inflammatory cell infiltration. There were 25 females and 12 males, aged from 21 to 48 yrs (mean 33.5±7.6 yrs). The age at onset of the disease was on average 26.1±6.0 yrs, ranging from 13 to 41 yrs. The symptoms began in the third decade in 64% of the patients (fig. 4). The duration of the disease ranged from 1 to 23 yrs, with a mean of 7.4±4.9 yrs. The parents of 14 patients were first cousins, and of 1, second cousins. Twelve patients in 7 pedigrees had family histories of a similar disorder. Another 2 patients were probably familial. Siblings with the disorder were observed in 1 family. The initial symptom was muscle weakness of the legs or gait disturbance in 33 patients (90%), weakness of the hands in 2, and weakness of both the hands and legs in 1. The neck flexor muscles were affected in 21 (68%) of the 31 well-described patients. In all patients, muscle weakness was predominantly seen in the distal muscles of the legs or diffusely, but quadriceps femoris was spared or only slightly involved in 9, and gastrocnemius in 4. The trunk muscles were affected in 6 patients, in whom the duration of illness was between 5 and 15 yrs (mean: 9.3±4.0 yrs). Most patients showed a combined waddling and steppage gait because the iliopsoas muscles were affected in addition to the distal muscles from an early stage.

Distal muscles in the arms were more severely affected than proximal in 15 patients, and proximal muscles predominantly affected in 5 patients. Clinical

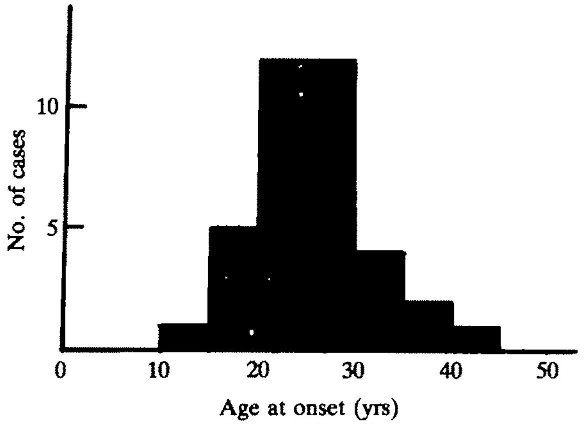

FIG 5 Distribution of age at onset of DMRV.

TABLE 1. REVIEWED CASES OF DMRV IN JAPAN

Authors	*Age (yrs)/ sex*	*Age of onset*	*Family history*	*Consan-guinity*	*Initial symptom*	*Neck*	*UL proc.*	*UL dist.*	*LL proc*	*LL dist.*	*Highest serum CK*	*EMG*	*NCV*
Mizusawa *et al.*, 1980	29/F	26	+?	—	Gait dis.	ND	—	++	++	++	×2.7	M	N
Inoue *et al.*, 1981	48/F	31	—	—	Weak legs	+	—	+	++	++	ME	Mn	N
Nishitani *et al.*, 1981	27/F	19	—	—	Weak legs	—	++	++	++	++	ME	M	N
Tashiro *et al.*, 1982	30/F	23	—	—	Gait dis.	+	+	+	++	++	ME	Mn	N
	41/M	28	—	—	Gait dis.	+	++	+	++	++	ME	Mn	NP
	26/M	24	—	—	Gait dis	—	+	+	++	++	ME	Mn	N
Kira *et al.*, 1982	27/M	26	—	+	Weak feet	—	—	+	+	++	×2.2	Mn	N
	21/M	13	—	+	Weak feet	++	++	+	++	++	×1.1	Mn	N
	25/F	18	—	+	Weak feet	+	+	++	+	++	×1.1	Mn	N
	32/F	25	—	—	Weak feet	+	—	++	+	++	×2.4	Mn	N
	44/F	33	—	+	Weak feet	+	+	++	++	++	×3.8	Mn	N
	31/F	27	—	+	Weak feet	+	+	+	+	++	×1.2	M	N
Kumamoto *et al.*, 1982	25/M	23	+	+	Weak legs	—	—	++	++	++	×2.7	Mn	N
	32/M	26	+	+	Foot drop	+	+	++	+	++	×2.7	M	N
	36/F	26	+	+	Weak legs	+	+	++	+	++	N	NP	NP
	35/F	30	—	—	Weak legs	—	—	++	+	++	N	M	N
Matsubara and Tanabe, 1982	25/M	22	+	+	Weak legs	—	—	—	—	++	×3.9	M	N
	30/F	24	+	+	Weak legs	—	+	++	+	++	×4.2	NP	ND

TABLE 1 (*continued*)

Nakanishi *et al*, 1982	44/F	34	+	—	Weak legs	ND	+	++	++	++	×1.4	ND	ND
1983	38/M	33	—	—	Weak legs	ND	+	+	++	++	×10.6	M	N
	21/F	18	—	+	Weak legs	ND	+	+	++	++	×1.8	ND	ND
	47/F	41	—	—	Weak legs	ND	+	—	++	++	×1.2	ND	ND
	42/F	38	—	—	ND	ND					×3.2	ND	ND
Tsukagoshi *et al.*, 1984	23/F	18	—	+	Gait dis.	—	—	+	—	++	×2.3	M	ND
	33/M	30	—	—	Gait dis.	++	+	++	—	++	×5.7	M	ND
	43/M	20	+	—	Weak hands	—	++	++	+	++	×3.4	M	ND
Mizusawa *et al*, 1986	32/F	25	—	—	Gait dis	+	+	+	++	++	×1.6	Mn	N
	48/F	38	—	—	Weak hands	+	+	+	++	+	×1.2	Mn	N
	43/F	27	+?	—	Gait dis.	—	—	+	++	++	×9.4	Mn	N
	33/F	26	—	—	Gait dis.	++	+	++	++	++	×2.7	Mn	N
	31/F	26	—	—	Gait dis.	++	+	++	++	++	×0.7	Mn	N
	26/M	25	—	—	Gait dis	+	+	++	++	++	×2.7	Mn	N
Present cases	33/F	22	+	+	Gait dis	++	++	++	++	++	×3.0	Mn	N
	34/M	25	+	+	Weak legs	++	+	—	++	++	×7.0	M	N
	35/F	20	+	—	Weak legs	++	++	++	++	++	×1.4	M	N
	37/F	24	+	—	Weak legs	++	++	+	++	++	N	Mn	N
	32/F	30	+	—	Weak legs	++	+	+	+	+	×2.5	Mn	N

UL = upper limbs; LL = lower limbs; Prox. = proximal; Dist = distal; ND = not described, M = myopathic change; NCV = nerve conduction velocity; NP = not performed, Mn = myopathic change with mild neuropathic change; N = normal, MD = mildly decreased, ME = mildly elevated; Gait dis = gait disturbance.

descriptions were available in 7 of 9 patients with a duration of illness of more than 10 yrs; 5 of them were nonambulatory. One patient with a 7 yr history of the disease was unable to walk. None showed weakness or wasting of the facial, extraocular, bulbar, or intercostal muscles or of the diaphragm. Two patients, aged 27 yrs and 21 yrs reported by Kira *et al.* (1982), had high-arched feet, and the former also had a high-arched palate. The serum CK levels were only mildly elevated or within normal limits,. but 2 patients described by Nakanishi *et al.* (1982, 1983) and Mizusawa *et al.* (1986) had high serum CK levels. Needle EMG examination disclosed myopathic changes with mild neuropathic changes in 19 patients, and only myopathic changes in 12. Nerve conduction velocities were within normal limits in 27 patients and mildly decreased in 1, of the available 28. In addition to numerous fibres containing rimmed vacuoles, the muscle biopsies of all patients showed marked variation in fibre size with endomysial fibrosis; atrophic fibres tended to be aggregated in small groups. There was no inflammatory cell infiltration, and necrotic fibres undergoing phagocytosis or regenerating fibres were rare or absent. Electron microscopic examination disclosed numerous myeloid or lamellar bodies and autophagic vacuoles containing cytoplasmic debris and glycogen particles. There was no increase in the number of satellite cells. In 3 patients, a 38-yr-old man and a 47-yr-old woman described by Nakanishi *et al.* and our Case 3 (the parents of 1 patient were first cousins and 1 had a positive family history) showed intranuclear filamentous inclusions (fig. 3c), and 4 cases except for a 47-yr-old woman described by Nakanishi *et al.* (1982, 1983) and a 25-yr-old man reported by Matsubara and Tanabe (1982) (2 of which were familial) showed intracytoplasmic filaments. Five patients, including 2 of ours, received prednisone without a clinical response, although 2 showed a decrease in serum CK levels. There were no differences between familial and sporadic cases with respect to clinical, laboratory or pathological findings.

DISCUSSION

Welander (1951) reported a distinct form of distal myopathy in 249 patients from 72 pedigrees. Muscle weakness and wasting were first noticed in the muscles of the hands and feet. There are several distinct clinical differences between Welander's disease and distal myopathy with rimmed vacuole formation (DMRV). The former is inherited as an autosomal dominant trait, and the onset is in late middle life, between 40 and 60 yrs of age. In the majority of patients the muscle weakness did not progress to proximal muscles. The disorder was not incapacitating and the neck and trunk muscles were not affected. The muscle pathology of Welander's disease showed fibre fragmentation, phagocytosis, fibre splitting, vacuolation, an increased number of central nuclei and type 1 fibre atrophy, but no fibres with rimmed vacuole formation (Welander, 1951; Dahlgaard, 1960; Barrows and Duemler, 1962; Edström, 1975; Thornell *et al.*, 1984) (Table 2).

Miyoshi *et al.* (1967, 1986) reported 17 patients with autosomal recessive distal

TABLE 2 DISTAL MYOPATHIES AND INCLUSION BODY MYOSITIS

	MDTH	*Markesbery et al., (1974, 1977)*		*ARDMD*	*DMRV*	*IBM*
Heredity	AD	Sporadic	AD	AR	AR sporadic	Sporadic familial
Female:male	1:1.5			1:1	2:1	3·5
Onset (yrs)	20–77	19 and 20	43–51	12–30	13–41	16–77
First symptom	Weak hands	Weak feet	Weak feet	Weak feet	Weak feet	Weak legs or arms
Clinical course	Very slowly progressive	Progressive	Slowly progressive	Progressive	Progressive	Slowly progressive
Weakness of the neck	—	—	—	—	+(68%)	+(23%)
Serum CK		Marked	Mild	Marked	Mild	Mild
EMG	Mn	M	Mn	M	Mn	Mn
Muscle pathology	M	M	M	Dystrophic	Mn	Mn
Rimmed vacuoles	+ or —	+	++	—	++	++
Inflammatory cells	—	—	—	—	—	+
Intranuclear filaments	—	—	—	—	+	+

MDTH = myopathia distalis tarda hereditaria (Welander, 1951), ARDMD = autosomal recessive distal muscular dystrophy (Miyoshi *et al.*, 1986); DMRV = distal myopathy with rimmed vacuole formation, IBM = inclusion body myositis, AD = autosomal dominant; AR = autosomal recessive; M = myopathic; Mn = myopathic with mild neuropathic changes

muscular dystrophy. Muscle wasting and weakness were marked in the distal parts of the legs, and the thigh and gluteal muscles became affected later. The clinical manifestations, however, differed in some respects from those in DMRV. In autosomal recessive distal muscular dystrophy the clinical course is more prolonged. The small hand and neck muscles are not affected. There is preferential involvement of the gastrocnemius and soleus muscles rather than the peroneal muscles. The serum CK levels are markedly increased and the muscle pathology shows numerous necrotic fibres with phagocytosis and an increased number of regenerating fibres, which are also observed in Duchenne muscular dystrophy (Nonaka *et al.*, 1985; Miyoshi *et al.*, 1986).

Markesbery *et al.* (1977) described 2 sporadic cases with early adult onset, who had distal muscle weakness of the legs, which later spread to proximal muscles. This disease is distinguishable from DMRV because the serum CK levels were markedly elevated (24 and 108 times the normal value) and the muscle pathology showed numerous necrotic fibres. The distribution of the involved muscles was also different from that seen in DMRV. The neck, iliopsoas and proximal muscles of the arms were not affected in patients with the illness for more than 7 yrs' duration. Two Japanese cases with high serum CK values (10.6 and 9.4 times the normal value) reported by Nakanishi *et al.* (1982, 1983) and Mizusawa *et al.* (1986) may be classified into the group of the sporadic distal myopathy described by Markesbery *et al.* (1974, 1977). However, serum CK levels seen in 2 patients of Markesbery *et al.* were more severely elevated. Markesbery *et al.* (1974, 1977) mentioned 6 patients in a family with another type of distal myopathy. Weakness was first noticed in the feet, and later in the hand, shoulder girdle, hip and trunk muscles. The patients became unable to walk. The serum CK levels were slightly elevated. These clinical features resemble those in DMRV, except that the neck muscles were spared and the mode of inheritance was probably autosomal dominant. The muscle pathology showed numerous necrotic fibres with phagocytosis, although fibres with rimmed vacuoles were observed.

Miller *et al.* (1979) reported 3 sporadic cases with slow progression of the weakness in the distal parts of the legs and later in the arms. De Visser (1983) described 3 sporadic cases with distal myopathy that affected only the legs. Scoppetta *et al.* (1984) mentioned 2 familial cases with wasting and weakness of the peroneal muscles. The symptoms appeared in adolescence or early adult life. In these patients the proximal muscles were spared or only slightly affected. The serum CK levels were markedly elevated and pathological examination of muscles revealed numerous necrotic fibres with an increased number of regenerating fibres. Magee and DeJong (1965) and van der Does de Willebois *et al.* (1968) described patients with an onset in childhood who noted leg weakness, especially of the anterior tibial and peroneal muscles, early in the course of the disease. The disorder, however, seldom involved more proximal muscles and inheritance was of autosomal dominant pattern. On pathological investigation of muscle, no fibres with rimmed vacuoles were seen. Sumner *et al.* (1971) described 6 patients in a family showing much variation in the clinical features, and Bautista *et al.* (1978) reported hereditary distal myopathy with an onset in early infancy. These patients differ from those with DMRV in the muscle pathology.

Rimmed vacuole formation in muscle fibres is not specific to distal myopathy. It has been recognized in various disorders (DiMauro *et al.*, 1973; Engel, 1973; Fukuhara *et al.*, 1980; Kozachek and Wilson, 1982; Lehmann *et al.*, 1986). Recently, Argov and Yarom (1984) reported 9 patients from 4 families with generalized muscle weakness with sparing of the quadriceps femoris muscles. The serum CK levels were within normal limits or only moderately increased, and the muscle pathology showed a typical rimmed vacuole myopathy. These patients, however, had no weakness of the neck muscles and only mild weakness of the deltoid and hand muscles. The mode of inheritance was autosomal dominant and EMG showed neuropathic changes. Chutkow *et al.* (1986) described relatives with an autosomal dominant myopathy, which was limited to the limb-girdle muscles. As to the muscle pathology, rimmed or autophagic vacuoles were the most characteristic feature. The serum CK levels were normal or only mildly elevated. These patients again showed no weakness of the neck muscles or distal limb muscles.

The muscle pathology of inclusion body myositis (IBM) features numerous fibres with rimmed vacuoles in addition to necrotic fibres with phagocytosis, regenerating fibres, adipose tissue replacement and fibrous tissue proliferation (Chou, 1967; Carpenter *et al.*, 1976, 1978; Chad *et al.*, 1982; Mikol *et al.*, 1982).

The degree of necrosis and regeneration varied from patient to patient (Danon *et al.*, 1982). In most cases, lymphocytic inflammatory cell infiltration is observed although this may be sparse or absent in some cases. In DMRV, most rimmed vacuoles had increased acid phosphatase activity. Carpenter *et al.* (1970) stated that the vacuoles in IBM did not show elevated acid phosphatase activity, but they were later demonstrated to have increased enzyme activity (Carpenter and Karpati, 1984; Banker and Engel, 1986). Intranuclear or/and intracytoplasmic filaments 15 to 18 nm in diameter are considered to be characteristic of IBM (Carpenter *et al.*, 1970; Ringel *et al.*, 1987). Filaments similar to those seen in IBM have been found in patients with DMRV (Matsubara and Tanabe, 1982; Nakanishi and Kuzuhara, 1983; Nonaka *et al.*, 1985) and other disorders (Fukuhara *et al.*, 1980). Yunis and Samaha (1971) and Tomé *et al.* (1981) suggested that the filaments observed in IBM could be muscle filaments. Some (Julien *et al.*, 1982; Sawchak *et al.*, 1983) have been uncertain whether the nuclear or cytoplasmic filaments are causally related to IBM, whereas Chou (1986) recently reported that in patients with IBM, mumps antigen was demonstrable both in intranuclear and cytoplasmic inclusions using an immunoperoxidase method, although it was not confirmed whether the filaments themselves were positive for mumps antigen. On the other hand, in DMRV the filamentous inclusions are widely considered to be a secondary phenomenon accompanying the process of atrophy of muscle fibres because the autophagic process has been assumed to be an essential degenerative mechanism in DMRV (Nonaka *et al.*, 1981; Nakanishi and Kuzuhara, 1983; Nonaka *et al.*, 1985; Ii *et al.*, 1986). Pathological examination of muscle, therefore, is not necessarily helpful for a differential diagnosis between IBM and DMRV. The serum CK levels and EMG findings are also not useful for differentiating these two disorders. IBM showed a well-delineated bimodal age spectrum with an onset in the second or sixth decades (Eisen *et al.*, 1983). Carpenter *et al.* (1978) emphasized that IBM lacks features of connective tissue disease, and is unresponsive to corticosteroid therapy. Nevertheless, steroid-responsive cases or cases with an associated connective tissue disease have been reported (Sato *et al.*, 1969; Marie, 1980; Chad *et al.*, 1982; Lane *et al.*, 1985). These findings suggest that IBM may be heterogenous. We reviewed reports of 40 patients with IBM, including 24 reviewed by Julien *et al.* (1982), and 19 reported by Mikol *et al.* (1982), Chad *et al.* (1982), Danon *et al.* (1982), Eisen *et al.* (1983) and Lane *et al.* (1985). Case 7 of Eisen *et al.* was omitted because of the positive family history. The age at onset was less than 40 yrs in 12 patients (6 males and 6 females), in the fourth decade in 5 (3 males and 2 females) and above 50 yrs of age in 23 (16 males and 7 females). The male to female ratio was 5 : 3 for all patients, and 1 : 1 for the younger group, in contrast to the considerable female predominance in DMRV. As an initial symptom, 14 patients, including 3 in the younger age group, had muscle wasting and weakness in the upper limbs, 16, including 4 in the younger group, involvement of the lower limbs, and 10, including 5 in the younger group, in both. On the other hand, 90% of the patients with DMRV had muscle weakness and wasting in the legs as an initial symptom. Sixteen patients (40%) with IBM showed dominant proximal involvement and 13 distal dominance, whereas most patients with DMRV showed distal or diffuse impairment in the legs. The neck muscles were affected in 10 patients (25%) with IBM, in contrast to the 70% with DMRV. Muscles of the trunk, which were later severely affected in DMRV, were not involved in IBM. IBM usually showed a prolonged benign course without nonambulatory cases. In IBM, dysphagia was seen in 5 patients, dyspnoea in 1, cutaneous rashes in 2 and an associated connective tissue disease, including Sjögren's syndrome, dermatomyositis and scleroderma, in 4. These signs were not recognized in any patient with DMRV. In addition, one-third of the patients with DMRV had a positive family history. These differing findings between IBM and DMRV strongly suggest that the two disorders are not the same, although there could be difficulty in differential diagnosis if the muscle pathology shows no necrotic fibres with phagocytosis or inflammatory cell infiltration. In order clearly to differentiate one from another, further investigations would be required.

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ABNORMAL SPATIAL PATTERNS OF ELBOW MUSCLE ACTIVATION IN HEMIPARETIC HUMAN SUBJECTS

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SUMMARY

The patterns of electromyographic (EMG) activity in spastic-paretic and contralateral elbow muscles of 10 hemiparetic human subjects were compared during a sequence of graded voluntary isometric contractions against 4 different-sized loads. These loads were orientated successively at 8 different angles over a 360° range, referenced to a plane at the wrist orthogonal to the long axis of the forearm. Comparisons of EMG activity recorded from normal and paretic limbs revealed that there were marked differences in the torque angles which evoked significant EMG activity, in the angular range of EMG, in the angle of peak EMG, and in the scaling of EMG magnitude with increasing isometric loads. In severely impaired limbs, there was a marked shift in both the peak EMG angle and the angular domain of EMG activity for both biceps and triceps muscle groups, away from the normal elbow flexion-extension axis towards external humeral rotation and shoulder girdle elevation. The extent of the disturbance in the spatial patterns of EMG activity was closely correlated with the clinical severity of the spastic-paretic disability, which was quantified using a functional scale patterned after that described by Fugl Meyer *et al.* (1975). The observed patterns of EMG activity in paretic flexor muscles do not conform with established synergistic patterns, such as might be released by excitation of the flexor reflex in a normal limb. Possible origins for the anomalous EMG patterns are discussed.

INTRODUCTION

A characteristic outcome of stroke is spastic hemiparesis, which is often associated with postural deformity of the paretic limbs and severe disruption of voluntary movement. Although there are detailed descriptions of the disturbances in movement that follow human hemiplegic stroke (Twitchell, 1951; Brunnstrom, 1970) and of the disturbances that follow broadly similar lesions of particular descending pathways in nonhuman primates (e.g., Lawrence and Kuypers, 1968*a*, *b*), there is surprisingly little known about the spatial distribution of activity among individual limb muscles of humans who have experienced a stroke, or even whether disturbances of muscle selection contribute to loss of torque generation

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across joints of spastic-paretic limbs. Most studies of muscular function in hemiparesis have focused on altered *temporal* patterns of electromyographic activity for selected muscles involved in voluntary movement or gait (Peat *et al.*, 1976; Conrad *et al.*, 1985; Knutsson, 1985). In the present study, we have examined the *spatial* distribution of muscular activity at the elbow during graded isometric contractions orientated systematically in a number of directions. The direction of elbow force was varied systematically over a 360° range, referenced to a plane orthogonal to the long-axis of the forearm. We chose to study isometric contractions (rather than movement) in order to minimize the complexity of the experiments, and for comparison with a data base recently established in our laboratory using normal human subjects (Buchanan *et al.*, 1986). We found that hemiparetic patients exhibited inappropriate spatial patterns of muscle activation, which were most evident in severely impaired limbs. These altered patterns consisted of changes in both the principal direction of activity and the angular range over which each muscle was active. Our observations may help to clarify the mechanisms underlying both the postural disturbances and incoordination of voluntary movement in paretic limbs of hemiparetic subjects. Portions of this material have been published in abstract form (Bourbonnais *et al.*, 1986).

METHODS

Population characteristics

Ten subjects with hemiparesis and 6 normal subjects were included in this study. Ages ranged from 34–68 (mean 61) yrs for paretic subjects, and 28-47 (mean 37) yrs for normals. All hemiparetic subjects had sustained cerebrovascular incidents, with the onset ranging from 1 to 15 yrs before the examination (mean of 5 yrs). EMG activity was recorded from the paretic limb in all 10 subjects, and from the contralateral limb in 7 of these 10. We recorded from the dominant arm of all 6 normal subjects. Spastic-paretic subjects were selected on the basis of the following criteria: (1) paresis in elbow muscles of affected limb; (2) spasticity if present, is confined to the paretic side; (3) absence of concurrent sensory impairment in the paretic limb; (4) absence of overt contracture; (5) absence of contralateral motor or sensory impairment (with respect to the paretic limb); and (6) absence of concurrent dementia or substantial cardiorespiratory impairment. Subjects were able to give informed consent.

Experimental arrangement

Subjects were seated in a heavy orthopaedic chair, which was adjusted to obtain the same upper body position for different subjects. The test limb was maintained in 45° of shoulder flexion and 90° of elbow flexion by an elbow sling, which was attached to an overhead bar (*see* fig. 1). (The sling was necessary because many paretic subjects were unable to maintain voluntary arm elevation for prolonged periods.) In addition, the forearm was kept in the fully pronated position in both normal and paretic limbs, because impaired subjects were unable to maintain alternative positions of the paretic limb for lengthy periods of time. Although full forearm pronation may not be the optimal position for biceps action, biceps activity in this position is still substantial (*see* Results). Moreover, we have also observed that for equivalent elbow flexion torque, EMG levels are only about 30% less in full pronation than in supination (*see also* Buchanan and Rymer, 1987, for a description of the effects of superimposed pronation/supination torque on biceps EMG activity).

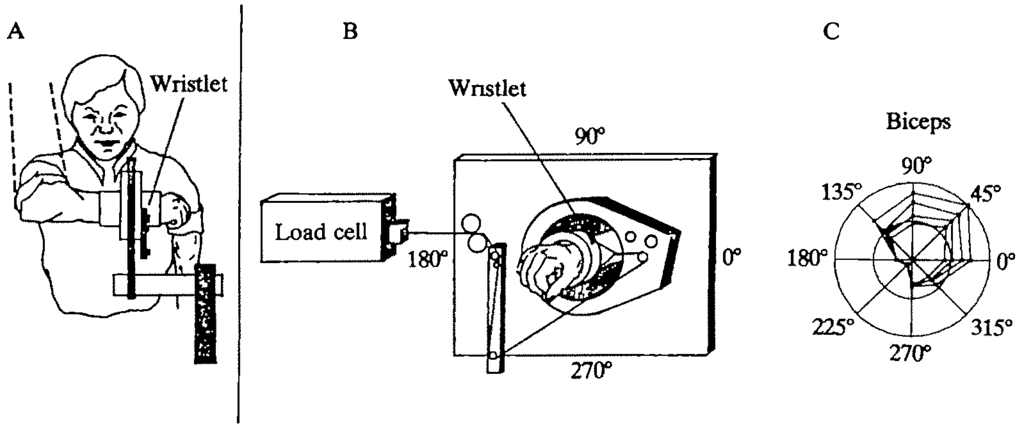

FIG. 1. Torque director and EMG polar plot for the biceps muscle A, positioning of the subject, and sling arrangement, B, configuration of pulleys and cable for an extension torque at 180°; C, polar plot used to summarize the surface EMG data from one of the test muscles, the biceps brachii The different directions of force generation are represented by the angular display (0–360°), with 45° being the primary flexion axis, and 225° the primary extension axis EMG magnitude increases along the radial axis. The outer ring is scaled to represent the maximum EMG activity for a given muscle while the inner ring is a 50% marker. Each of the four contours represents the EMG response to one force level (*see* text for details).

Subjects wore a velcro band on the lower forearm, immediately proximal to the wrist (fig. 1A, B). This band was attached to a 'Sensotec' load cell via a nonextensible cable that passed around a sequence of pulleys. To minimize undesirable movements of the trunk and shoulder, a harness strapped them to the vertical support of the orthopaedic chair. Positioning of the shoulder, elbow and forearm were under the voluntary control of the subject, who was instructed to generate force with as little limb movement as possible. Fig. 1B shows that by changing pulley arrangements, the force direction could be varied over 8 directions traversing a 360° range, referenced to a plane proximal to the wrist, orthogonal to the long axis of the forearm. Because of the lowering of the humerus to 45°, the flexion extension axis of the elbow traverses the line from 45 to 225°. Forces generated in directions orthogonal to the plane of motion of the elbow (i.e., at 135 and 315°) originate primarily in the shoulder, and the elbow is then used as a passive link, or strut, in which forces are borne largely by ligaments and joint contact areas (*see* Buchanan *et al.*, 1986). For other directions, the forces recorded by the load cell are largely generated at the elbow; however, transmission of force from the shoulder and axial musculature may have occurred during extreme effort, especially in severely impaired subjects.

In all 16 subjects (10 hemiparetic, 6 normal), activities of three muscle groups (biceps brachii, lateral head of triceps brachii and brachioradialis) were recorded simultaneously by surface electrodes, taped on the skin surface over the muscle belly. In addition, for 1 normal subject, recordings were made of the same 3 muscles using surface and intramuscular electrodes simultaneously. In 7 hemiparetic subjects, we also recorded the activity of the brachialis muscle with surface electrodes; however, these results will not be described in any detail because there was some possibility of recording EMG activity (cross-talk) from adjacent muscles. Placement of electrodes conformed with positions recommended by Delagi and Perotto (1980).

Electrodes were 1 cm platinum coated discs, mounted with their centres set 3.5 cm apart. These discs were attached to small preamplifiers (Motion Control Inc.), with gains of 375, and bandwidths of 10 Hz–10 kHz. EMG signals were then further amplified (100–500), and low-pass filtered at 100 Hz to prevent aliasing during computer acquisition. Intramuscular recordings for 1 subject were obtained using pairs of 75 μm, teflon coated stainless steel wires, bared over the terminal 3 mm, and inserted with hypodermic needles. To evaluate cross-talk in either surface or intramuscular electrodes, we routinely performed tests inducing selective muscle activation (Kendall and McCreary, 1983). Recordings contaminated by significant EMG activity from adjacent muscles were improved by repositioning the electrodes.

Data recording and analysis

Limb force (recorded from the load cell) and EMG recordings were sampled by analog-to-digital converters at 5 ms intervals and the values recorded in the memory of a PDP 11/73 computer. Data records were stored on hard discs (RL02) for later evaluation and processing. In the course of this analysis, EMG recordings were full-wave rectified digitally, and the mean rectified EMG and force values calculated from each trial, using a 600 ms window in which force was stable. Records in which there was a significant trend or instability of the force trace were excluded from further evaluation.

Experimental protocol

During the experiment, subjects were given visual feedback of the isometric force they exerted, as well as a target specifying the requested force level. Subjects were instructed to match the target level for a period designated by the computer, typically 2.5 s. Subjects were also instructed to maintain the degree of pronation, and to allow as little movement of the trunk, shoulder and elbow as possible.

Targets were presented randomly to the subject. Two load ranges were available (low: 4.4, 8.9, 13.3, 17.8 N; or high: 4.4, 13.3, 22.9, 28.9 N) with the range chosen to match the strength of the particular paretic limb. Each experiment required that muscle activity be recorded in 8 directions, at 4 different force levels, with 5 repetitions at each level, making 160 trials in all. Trials were discontinued when subjects were unable to maintain a particular force level for the required interval, or were unable to generate significant force for particular directions. Substantial rest periods were included to minimize fatigue.

Clinical evaluation

The motor function of the upper limb in the hemiparetic subjects was tested with a procedure based upon that described by Fugl-Meyer *et al.* (1975). This testing included an evaluation of tendon reflexes, together with a performance evaluation of proximal and distal voluntary movement of the arm. Cumulative scores approaching 60 for the upper limb represent near-normal motor performance, while low scores (< 20) indicate severe disability. On the basis of the distribution of Fugl-Meyer scores, we divided our subjects into severely impaired (< 30) and moderately impaired (> 30) categories. Muscle tone was evaluated on a six-point scale (0 = normal tone; 5 = severe spasticity) with modified Ashworth criteria (Ashworth, 1964; Pedersen, 1969), and the active range of motion for elbow flexion-extension, and forearm pronation-supination was measured with a goniometer.

RESULTS

We compared the patterns of EMG activation in elbow muscles of paretic and contralateral arms of 10 hemiparetic human subjects, during a series of graded voluntary isometric contractions whose directions were varied systematically over a 360° range.

Characteristics of the polar plot

We will first describe the characteristics of the muscular 'polar plot' (*see also* Buchanan *et al.*, 1986), which summarizes the relation between mean rectified EMG levels for a given muscle and joint force direction, over a range of increasing isometric forces. Fig. 1c, taken from a normal subject, shows a typical EMG polar plot for the biceps brachii muscle, recorded with surface electrodes during isometric force generation at the elbow joint. Points plotted along the radial axis reflect the magnitude of mean rectified EMG, while the angular orientation of the radial axis corresponds to the direction of joint force. The radial axes reflect the 8 directions in which force was generated. Since the shoulder is set at 45° of flexion (*see* Methods), elbow flexion-extension is indicated by the axis extending from 45 to 225°.

The polar plot shows that substantial increases in biceps EMG, reflected in the radial amplitude, are recorded for forces ranging in direction from 135° to 315°. Since the EMG points are distributed at approximately equal increments from each other along each radial axis, and since forces are generated in equal increments, the form of the EMG force relation for biceps is approximately linear in each direction in which the muscle is active. (This claim is not directly documented here, because force does not appear explicitly in the polar plot.) Furthermore, since EMG scaling is evident on all four radial axes in which substantial biceps EMG was generated, an approximately concentric series of contours results. This contour, or 'polar' plot provides a valuable summary display of muscle activation patterns in different directions for voluntary isometric contractions at the normal elbow joint.

The biceps polar plot depicts several important features of muscle use at the elbow which are pertinent to any evaluation of disturbances arising in the hemiparetic limb. These features include the following. (1) *Angular range.* EMG activity is substantial for an angular range of approximately 180°, extending to either side of the maximum at 45°, including directions in which no movement of the humeroulnar or radioulnar joints at the elbow is feasible, that is, EMG activation is not confined to the plane of motion of the elbow joint. A low level of EMG activity is also often present beyond the 180° range. (2) *Shape of polar plot.* The plot is broadly symmetric, and shaped like a distorted semicircle, with the peak EMG located at an angle appropriate for optimum mechanical effect (*see* below). (3) *Peak EMG.* The angle of peak EMG activity for the biceps is at 45 degrees, which corresponds to the plane of elbow flexion in this experiment. (4) *EMG scaling.* The effects of scaled increases in force are seen as a scaled series of concentric EMG contours. This pattern of EMG activity indicates that for this elbow joint angle and range of force levels at least, there are no alterations in the pattern of muscle selection with increasing force, such as selective recruitment (or derecruitment) of particular muscles at high force levels. If there was recruitment of some new muscle at high force levels, the form of the EMG polar plot would then change, displaying a modification in the semicircular shape, and a loss of the concentric scaling.

These features of the polar plot, namely 180° range, broadly semicircular shape, peak EMG value in the direction of optimum mechanical effect, and scaling with increasing force, are also evident in other muscles acting at the elbow, including the triceps brachii, and the brachioradialis (*see* below, and Buchanan *et al.*, 1986). The brachialis muscle polar plot was quite similar to that of biceps, although this is not illustrated here.

Comparison of intramuscular and surface EMG recording in normal subjects

To establish the selectivity of surface EMG recordings, we compared simultaneous recordings of surface and intramuscular EMG activity in 1 normal adult subject. Our findings are depicted in fig. 2 which shows surface and intramuscular EMG polar plots for biceps brachii, brachioradialis and triceps brachii. A detailed comparison of the two data sets shows that the biceps intramuscular plot is virtually identical in angular range, peak angle, shape, and scaling properties with the surface plot, and there are only minor differences apparent in the surface and intramuscular polar plots for the brachioradialis and triceps brachii. Taken overall, the difference between surface and intramuscular recordings is quite modest, providing firm justification for use of surface recordings in this study.

Comparisons between muscles in paretic and contralateral limbs

We compared polar plots for biceps, triceps and brachioradialis muscles in paretic and contralateral limbs of the *same* hemiparetic subject. This approach

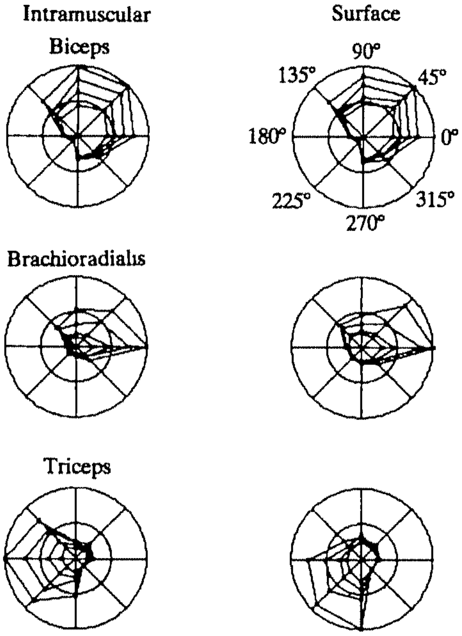

FIG. 2. Comparison of intramuscular and surface EMG polar plots from a normal subject. Polar plots are constructed as in fig. 1c Simultaneous recordings were made from biceps, brachioradialis and triceps muscles.

was selected because, in the absence of contralateral neurological disturbance, the patterns of muscle activation in contralateral limb muscles should provide the most accurate basis for comparison. To satisfy the requirement for absent contralateral disturbance, we restricted our study to hemiparetic subjects with no clinically discernible motor or sensory abnormality of the contralateral limb (*see* Methods). The adequacy of our selection procedures is validated by the close similarity between recordings taken from our 6 normal subjects (*see also* Buchanan *et al.*, 1986) and from contralateral limbs of hemiparetic subjects.

Fig. 3 compares the polar plots for three muscle groups, the biceps, triceps and brachioradialis, recorded sequentially from paretic and contralateral elbow muscles of 1 subject (Case 8, Table 1), with a moderately severe spastic hemiparesis. The load magnitudes were chosen so as to be accessible by the paretic limb; equal loads were then applied to the contralateral limb. As in fig. 2, the polar plots are again scaled so that maximum EMG activity reaches the outermost ring in each plot.

Comparisons of the EMG polar plots in paretic and contralateral limbs shows

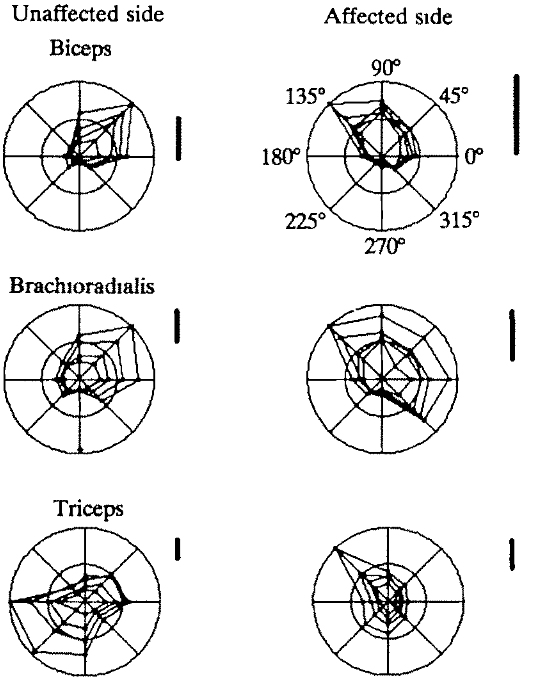

FIG 3. Comparison of surface EMG polar plots from the unaffected and affected limbs of the same hemiparetic subject (*Case 8*). Plots are constructed as in fig. 1c, using the same load range on each side (17.8 N). Calibration bars represent the EMG values (in mV) measured in the direction of maximum activity at the highest load. Calibration bars for biceps were 1.3 mV and 0.72 mV (paretic, unaffected), 0.63 mV and 0.42 mV for brachioradialis, and 0.17 mV and 0.15 mV for triceps. Electrode placements, amplifier gains and filter settings were essentially identical on the two sides, so that the calibration bars provide an accurate relative measure of the EMG levels required to achieve the maximum load attempted.

that there are significant differences in the angular range, in the shape, in the direction of peak activity, and in the scaling of EMG magnitude with increasing loads. Beginning with biceps in the paretic limb, the polar plot is now quite asymmetric and its domain is rotated counterclockwise, towards elbow extension. The direction of peak EMG activity in biceps is especially disturbed, now rotated to 135°, which is approximately 90° away from the 180 to 225° range of peak EMG recorded on the contralateral side. Moreover, the scaling properties are less clearly defined than in the normal limb, in that the orderly concentric arrangement of polar plots is also disrupted.

Broadly similar disturbances are also evident for the brachioradialis in the paretic limb. The peak EMG is rotated to 135°, and there is also an alteration in shape, with considerable broadening of the range of EMG activity, so that significant levels of EMG activity are now present well into elbow extension. One difference from the affected biceps is that much greater levels of EMG persist in the primary flexion direction, 45°.

The alteration in the triceps EMG polar plot is also significant, in that there is a 45° shift in the peak EMG value, from 180° to 135°, and an even greater shift in the force angles displaying substantial EMG activity. It is also of interest that the peak EMG arises at 135° in all of the muscles depicted. Finally, the polar plots for brachioradialis and triceps also appear to have lost the orderly concentric arrangement that is characteristic of normal muscles.

Differences in EMG magnitude between spastic and contralateral limbs (for Case 8). Since the EMG electrode placements and amplifier gains for the subject of fig. 3 were closely matched in each limb, estimates of EMG magnitude are of direct value in evaluating the relative strengths of the motor command to paretic and contralateral muscles. The EMG calibration scales in fig. 3 depict the EMG levels required to reach the maximum force attempted, which was the same on each side. The peak EMG in biceps, attained at 135°, was almost 2.0 times greater on the paretic side, but the ratio was actually near 1.0 for the primary flexion direction (45°).

The brachioradialis pattern was somewhat different, in that both the peak EMG and the 45° level were significantly greater on the paretic side. The triceps pattern was broadly similar to that of biceps, in that peak EMG levels were much greater on the paretic side, but the level at 225° was close to 1.0. The issue of force-EMG relations is taken up further in Results.

Polar plots in subjects with different degrees of impairment

Based on our functional evaluation of the severity of spastic-paretic disability, our group of 10 subjects was subdivided into a severely impaired category with Fugl-Meyer scores < 30 ($n = 5$), and a moderately impaired category with scores > 30 ($n = 5$).

Fig. 4 depicts polar plots for 3 subjects, representing the range of clinical severity of the hemiparesis in our sample group. Fig. 4A is recorded from a subject with

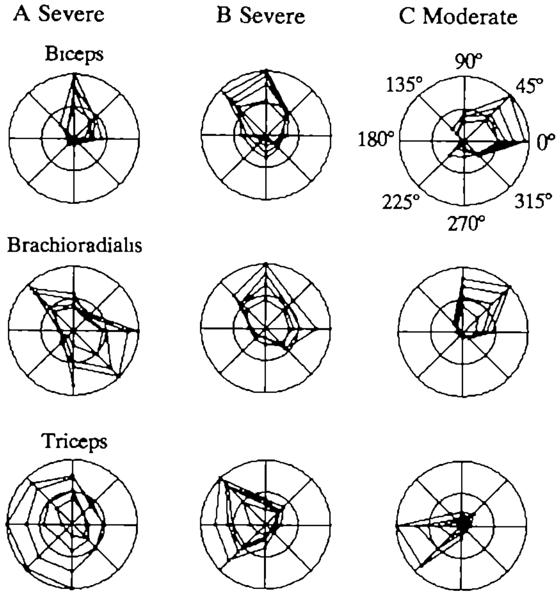

FIG 4. Comparison of surface EMG polar plots for spastic-paretic subjects with different levels of impairment Plots are constructed as in fig 1C A represents polar plots for three muscles from the affected limb of a severely-impaired subject (*Case 3*). B shows plots from a second severely-impaired subject (*Case 7*) The subject in C is the least severely affected (*Case 10*)

severe spastic hemiparesis, and almost no residual functional capacity, as assessed by the Fugl-Meyer scale (Case 3, Table 1). A comparison with the normal biceps brachii pattern of fig. 2 shows that the biceps polar plot in fig. 4A is now very narrow, with the peak rotated upwards in the direction of external humeral rotation. There is again a disturbance of orderly scaling, in that there is almost no increase in EMG with increasing force in the 45° direction.

The brachioradialis plot of the subject in fig. 4A is even more severely disrupted, displaying a novel 90° downward shift (with respect to the typical normal limb), and a secondary region, pointing well into extension. The combination of these two zones of brachioradialis activity gives rise to a very broad zone of activation, extending almost over the full 360°. Since the brachioradialis exerts no extension force, its activity orientated towards 135° is clearly a form of anomalous cocontraction. There is again little increase in EMG with increasing flexion force at 45°. Finally, the pattern of activation of the triceps brachii for our severely impaired subject (fig. 4A) is also modified, in that the angular range of EMG activation is extended, reaching into flexion, although the level of flexion EMG activity is modest.

Fig. 4B depicts the polar plots from a subject with severe hemiparesis (Case 7, Table 1), in whom the disturbances of the polar plot are less extreme than that of Case 3. The biceps polar plot is again rotated upwards, but it is not quite as narrow as that in part A, and there is now substantial activity at 135°. For the primary flexion direction, 45°, there is virtually no increase in EMG with increasing force. The brachioradialis plot is also distorted in that the range of EMG activity extends upwards to 135°, and to 135° in the downward direction. The triceps range approximates that seen in the normal, but the peak EMG is shifted upwards to 135°. In contrast, the characteristics of the polar plots from a moderately impaired subject in fig. 4C (Case 10, Table 1) are close to the normal, with the possible exception of the triceps brachii polar plot, which appears to be narrower than that recorded in most normal subjects.

EMG magnitude in spastic and contralateral limbs (fig. 4). The absolute magnitude of biceps EMG activity varied substantially between spastic-paretic and contralateral limbs of the three illustrated subjects. For the severely impaired subject of fig. 4A, biceps EMG in the impaired limb was markedly reduced in several flexor directions. For example, at 45°, the biceps EMG was actually 3.3 times smaller on the spastic side. This biceps EMG reduction was not accompanied by any increase in EMG activity of the two primary synergists, the brachioradialis and brachialis. In contrast, for Case 7 (fig. 4B), who was less severely impaired, biceps EMG was considerably enhanced at 45° on the spastic side (1.93 times greater), with a modest reduction in EMG of brachioradialis (ratio 0.59) and brachialis. EMG scaling differences for other muscle groups were less marked. For Case 10 (fig. 4C), who also had mild impairment, EMG scales were closely comparable for all muscles on the two sides.

Population summary

The angular range and peak angle of EMG activation in the biceps and triceps muscles is summarized in fig. 5 for all hemiparetic and contralateral limbs studied. To facilitate quantitative comparisons between subjects, we designated EMG levels to be 'significant' for a given force direction if the EMG exceeded 50% of the maximum value for at least two force levels. (These levels would appear as two or more radial points beyond the inner ring of the polar plot.) In fig. 5, the open circles denote significant EMG activity, while the closed circles indicate the direction of maximum activity for each muscle. The hemiparetic population of 10 subjects is again divided into severely paretic ($n = 5$), and moderately paretic ($n = 5$) groups, demarcated by the horizontal line in each plot.

Fig. 5A shows that biceps activity in 7 unaffected limbs extends from 0 to 90°, with the peak EMG (closed circles) located at 45°, a location quite appropriate to induce elbow flexion in a limb held at 45° of shoulder flexion. (EMG activity in the unaffected limb was not recorded in the remaining 3 subjects). Part B shows that triceps activity in 6 contralateral limbs ranges from 135 to 270°, with a maximum EMG value at either 180 or 225°, angles again appropriate for optimum mechanical effect for the elbow extensor.

Fig. 5C shows that biceps EMG activity in paretic limbs varies greatly in range of activation, in the location of substantial EMG activity, and in peak orientation.

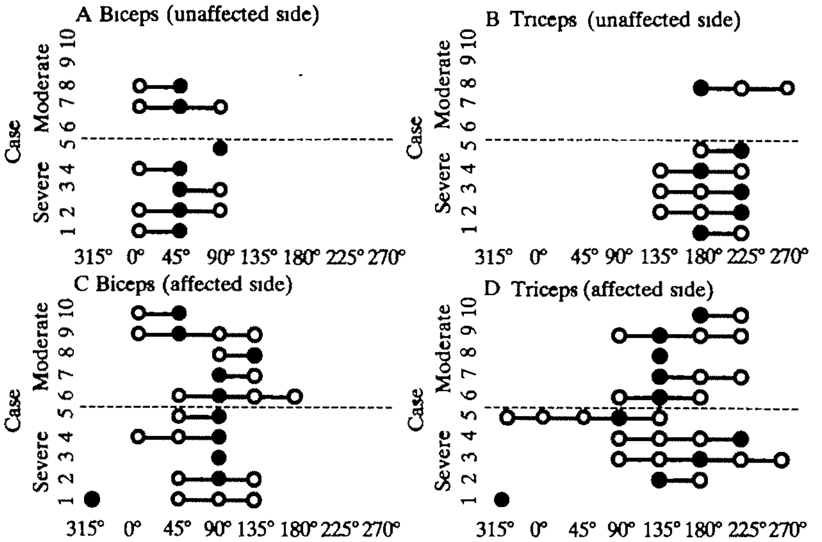

FIG. 5. Range of peak angles of EMG activity in biceps and triceps muscles for all unaffected and affected limbs tested from our patient population. Subjects are organized from most impaired (1) to least impaired (10), as in Table 1. A and B show the angular range (open circles) and directions of maximum EMG activity (closed circles) for these muscles from the unaffected limbs C and D illustrate the same measurements for muscles of the affected limbs.

In 3 of 10 cases, angular range is increased to 180° or more. In 7 subjects, the whole biceps polar plot is systematically shifted towards external humeral rotation, and the peak of biceps EMG activity is also shifted, with an obvious clustering about the 90° angle. This shift is again most obvious in the severely impaired subjects (lower portion of 5C).

As shown in fig. 5D, the angular range, orientation and peak EMG for the triceps also varies with the severity of the paresis. For the most severely affected subjects (lower portion of 5D), the orientation of EMG activity is quite variable, and EMG activity extends for 180°. In contrast, for unimpaired limbs, plots extended over a range of 90°. While there are variations in location of peak EMG activity in both normal and paretic limbs, there is a broad shift of the peak in the paretic limb towards 135°, an angle well away from the normal 180 to 225° location recorded in the unimpaired limb.

The brachioradialis muscle in the 6 unaffected limbs showed an angular range of 90°, centred around a peak at 45 or 0°. In all 5 severely impaired hemiparetic subjects, brachioradialis angular range increased to 135° or more, and the peak brachioradialis EMG was rotated downward to 315° (4/5 cases) or even to 270° (1/5).

EMG-force relations in the hemiparetic group

To evaluate the efficacy of muscle action in spastic and contralateral limbs, we calculated the ratios of EMG activity for one moderate force level, in a direction appropriate to the muscle under consideration. In 4/5 severely impaired subjects, the magnitude of biceps EMG in the spastic-paretic limb was significantly diminished at 45°, so that the ratio of paretic/contralateral EMG was substantially less than 1.0. (Actual ratio values for the 5 subjects were 0.33, 0.33, 0.35, 0.59 and 0.99.) The mean quotient was 0.52 ± 0.29 (SD). For 3 moderately impaired subjects studied, the mean biceps quotient was 1.51 ± 0.59 (SD).

EMG ratios for brachioradialis at 45° were also significantly different in severely impaired and moderately impaired subjects. The quotients were 0.82 ± 0.37 SD in severe cases (n = 5), and 1.27 ± 0.98 for moderately impaired subjects (n = 3). EMG ratios for triceps muscles were not significantly different on the two sides (1.18 ± 0.53) for either severe or moderately impaired subjects.

Clinical correlates

The severity of the paresis, of the postural deformity, and of the spasticity varied greatly over our subject sample, enabling potentially helpful correlations to be sought between the severity of the clinical disability and the polar plot disturbances. To simplify between-subject comparisons, we focused our attention on activity of the biceps and triceps brachii muscles as characteristic flexor and extensor muscles of the elbow.

Table 1 summarizes the major clinical features of our 10 hemiparetic subjects, with the subjects ranked in order of increasing functional capacity. Functional capacity was determined using the Fugl-Meyer scale, described in Methods. This scale was compared with a counter (summarized in the inappropriate muscle activity column of Table 1) which summed two types of error in the patterns of

TABLE 1 CLINICAL DATA FOR SPASTIC HEMIPARETIC SUBJECTS*

	Spasticity			*Active ROM*				*Functional evaluation*	*Inappropriate muscle activity*
Case	*Flex*	*Ext*	*Total*	*Flex*	*Pro*	*Sup*	*Total*	*(Fugl-Meyer)*	*score*
1	3	3	6	0	0	0	0	16	14
2	3	3	6	120	20	0	140	19	8
3	3	3	6	40	80	0	130	19	12
4	3	2	5	0	90	90	180	20	13
5	3	3	6	120	0	70	190	21	12
6	2	1	3	120	65	90	270	35	9
7	3	3	6	120	5	90	215	37	8
8	2	1	3	120	90	90	300	40	10
9	2	1	3	120	90	90	300	60	4
10	2	1	3	120	90	90	300	60	4

* Subjects are ranked from most impaired (1) to least impaired (10) based on a functional evaluation (penultimate column) following the procedure of Fugl-Meyer. The degree of spasticity was assessed on a 6 point scale (0 = normal tone; 5 = severe spasticity) for elbow flexion and extension 'Total' columns represent a summed score for each respective measure. Active range of motion (ROM) was evaluated for elbow flexion (0–120°; Flex), forearm pronation (0–90°; Pro) and supination (0–90°; Sup). The last column represents a measure of errors in muscle activity counted from the polar plots. The smaller the number, the fewer errors made in muscle activation (*see* text for details)

muscle activation, both extracted from the polar plots. In the first type, a counter is incremented whenever the subject fails to activate the muscle in the 'normal' direction, where normal is defined on the basis of the range shown by contralateral limb muscles in hemiparetic subjects (fig. 5A, B) and by normal controls. For the second type of error, the counter is incremented each time a spastic muscle generates substantial activity (i.e. ⩾ 50% of maximum) outside the mean angular range shown by contralateral limbs.

Determination of both types of error was based on the observations, summarized in fig. 5, that the biceps muscle generates substantial EMG activity (again ⩾ 50% of maximum) for the angles 0, 45, and 90°, whereas the triceps is significantly active for the 135, 180, and 225° elbow force angles. The last column of Table 1 represents the sum of these two types of error. The table also summarizes the essential clinical characteristics of the sample group, with respect to severity of spasticity, active range of movement and the Fugl-Meyer score.

Table 1 shows that subjects with the lowest functional evaluation scores, 16–21 (Cases 1–5) had the greatest severity of spasticity (reflected in the total spasticity score), the lowest total range of active motion, and the largest scores of inappropriate muscle activity (although there is clearly variation in these relations). We observed no particular relation of functional score or of the error 'counter' to age or duration of illness.

Table 2 evaluates the relations between the various columns in Table 1, using Spearman's coefficient of rank correlation. The table shows that there are significant correlations between the scores quantifying inappropriate spatial patterns of muscle activity and the Fugl-Meyer scores. Since these scores decrease with increasing disability, the value of the Spearman's coefficient is negative. A significant correlation is also observed between the score of inappropriate muscle activity and the total range of active motion of the elbow. There is no significant relation between muscle tone and the muscle activity score, although tone is significantly correlated with motor function (i.e., Fugl-Meyer and range of motion) of the spastic arm.

TABLE 2 SPEARMAN CORRELATION COEFFICIENTS[1]

	Fugl-Meyer	*ROM (total)*	*Tone (total)*
Fugl-Meyer	—	—	—
ROM (total)	0.964 $P < 0.001$ ***	—	—
Tone (total)	−0.637 $P < 0.046$ *	−0.732 $P < 0.016$ **	— —
Inappropriate muscle activity	−0.739 $P < 0.014$ **	−0.661 $P < 0.036$ *	0.486 $P > 0.152$ (n.s.)

[1] Categories relate to information presented in Table 1. Fugl-Meyer identifies the functional evaluation scores. The range of motion (ROM) and tone (Spasticity) scores were taken from the Total columns in Table 1 Probability scores are evaluated as not significant (n.s.) to highly significant (***)

DISCUSSION

The key findings of this study are that the shape, directional orientation, angular range and angle of peak activity in the EMG polar plots are severely disrupted in paretic elbow muscles of spastic hemiparetic subjects. Moreover, the disturbances in EMG polar plots correlate broadly with the severity of the clinical disturbance, in that severely impaired limbs display more extreme modifications of orientation, shape and range of their EMG polar plots than do moderately impaired limbs.

Earlier electromyographic studies in spastic limbs

To date, most of the published reports describing EMG patterns in limbs of hemiparetic subjects have dealt either with temporal disturbances of leg muscle activation during gait (e.g., Peat *et al.*, 1976; Knutsson and Richards, 1979; Knutsson and Mårtensson, 1980; Dietz *et al.*, 1981; Conrad *et al.*, 1985), or with temporal characteristics of EMG activity in arm muscles during either rapid voluntary movement or external perturbations (e.g., Angel, 1975; McLellan, 1977; Sahrmann and Norton, 1977; Hallett, 1979; Mizrahi and Angel, 1979; Berardelli *et al.*, 1985). To our knowledge, there has been no comprehensive description of the spatial patterns of activity in different muscles in spastic-paretic limbs.

Analysis of EMG activity in subjects with lesions of differing severity

It is noteworthy that the magnitude of EMG activity in various flexor muscles was systematically different in severely impaired and moderately impaired hemiparetic subjects (when compared against the contralateral biceps of the same subject), suggesting that different neural control strategies may have been used for force generation in each case.

In moderately impaired subjects, there was often a relative *increase* in biceps EMG activity in the paretic limb (e.g., Case 7, fig. 4) with no commensurate reduction in the activity of the other recorded synergists, brachioradialis and brachialis. Such EMG increases could indicate a disturbance of motor unit activation patterns in the paretic muscles (as described in Tang and Rymer, 1981) or a redistribution of load between different elbow flexors. Although we do not have EMG recordings from all the torque generating muscles, we have no evidence of a systematic redistribution in muscle activation, in which biceps EMG increases were coupled with reductions in brachioradialis and brachialis. For this reason, we would currently favour a disturbance in motor unit activation patterns as the most likely explanation for our findings in the mildly impaired subject group.

In contrast, for the severely disabled subject (e.g., fig. 4A), EMG activity in the impaired biceps was markedly *reduced* at 45° (in comparison with the contralateral side), and even peak EMG levels were also diminished on the paretic side. Although there was also a substantial change in the range and peak orientation of the brachioradialis polar plot (as in Cases 7, 8, figs 3, 4), there was no systematic enhancement of brachioradialis or brachialis EMG in the primary flexion direction (45°), which would have indicated that regular muscle 'substitution' took place.

What then is the alternative source of force at the 45° angle? Our observations suggest that there may be significant force contributions from several sources, including not only active flexor muscles, but also passive elements, such as joint capsule, ligaments and joint contact forces. These passive elements appear to behave as a 'strut' transmitting forces originating at the shoulder.

Use of a 'strut' to sustain elbow torque is applicable only if there is some motion of the limb, allowing the strut to be loaded. Although the shoulder and wrist were stabilized, some limb motion sufficient to load elbow flexors was possible, most often by elevation and retraction of the shoulder. Forces inducing elevation and retraction probably originated in shoulder musculature, a supposition supported by recordings from trapezius and deltoid muscles on the paretic side, which showed a strong, broadly orientated excitation in all 8 hemiparetic subjects examined.

In the moderately impaired subject, the 'strut' effect is probably achieved with the help of actively stiffened elbow flexor muscles, while in the severe case, joint capsule, muscles suffering from contracture, and joint contact forces may substitute. The likelihood of abnormal mechanical properties for spastic-paretic elbow muscles has been reported in a recent publication from this laboratory (Lee *et al.*, 1987), and similar changes have also been reported in spastic-paretic ankle muscles (Dietz *et al.*, 1981; Hufschmidt and Mauritz, 1985).

Finally, in severely impaired subjects there was often a loss of orderly scaling of EMG polar plots, so that increasing torque levels were associated with very little EMG increase in the primary flexor direction (e.g., fig. 4A), or even intersecting contour plots (fig. 3, biceps plot). This loss of orderly scaling was especially prominent at higher torque levels, and may have reflected varying degrees of cocontraction of flexors and extensors. (Note the extended ranges of brachioradialis and triceps polar plots.)

Disturbances of polar plot orientation

It is conceivable that the relative increase in biceps EMG at 90° is a reflection of unusual difficulty in elevating and externally rotating the humerus, arising because of weakness of shoulder stabilizing muscles. Increased biceps EMG activity could then reflect the action of the long head of biceps, helping to stabilize the head of the humerus in the glenoid fossa. While this explanation may account for the enhancement at 90°, it would not account for the abnormal scaling in the primary flexor direction, and it is therefore insufficient to explain the overall disturbance.

Alternatively, the neural strategies for activating biceps may now be modified, so that biceps activation is possible only in association with shoulder elevation and retraction. This activation could reflect alterations in voluntary strategy, the utilization of residual undamaged descending pathways (*see* below), the action of intersegmental reflexes (coupling muscles of the arm and shoulder), or reflexive responses to excessive loading of the joint capsule or ligaments. We do not yet know which, if any, of these factors are important.

'Synergies': a reassessment

The patterns of motor activity that emerge during recovery from hemiplegic stroke have been classified as flexor or extensor 'synergies' (Twitchell, 1951; Brunnstrom, 1970), based on their apparent resemblance to flexion withdrawal and crossed-extension reflexes elicited in the spinalized cat or dog (Sherrington, 1910) and in spinal man (Hagbarth, 1960). The outcome of the present study is that the patterns of EMG activity in spastic-paretic limbs do not appear to be directly analogous to a flexion-withdrawal response. Although we have presented no records of flexion reflex responses in our sample population, we would expect that any flexion reflex-mediated EMG patterns would follow the distribution reported in animal models, in which EMG activation promotes *flexion in the normal plane of joint motion*. It follows, further, that in a flexion reflex, EMG spatial patterns in the paretic limb should broadly resemble those seen in the normal (or contralateral limb), in which biceps, brachioradialis and brachialis are maximally activated at (or close to) the normal plane of joint motion (here 45°). Since maximal EMG activation in the paretic limb takes place about 90° away from the plane of elbow motion, it appears that, rather than representing a flexion 'synergy' in the Sherringtonian sense, the EMG patterns may be unrelated to any established normal pattern.

Role of descending neural pathways

On the basis of observations in nonhuman primates (Tower, 1940; Kuypers, 1960; Phillips and Porter, 1964; Petras, 1968; Lawrence and Kuypers, 1968*a*, *b*; *see also* Kuypers, 1982), it appears that corticospinal input is necessary for independent force generation across various limb joints, especially in distal joints of the upper limb. There is less information as to why particular muscles or muscle groups are selectively impaired in primates, and we have essentially no information regarding the neurophysiological substrates of the motor disability in man. However, based on the results of primate studies, it is likely that the stroke disrupts corticospinal and corticobulbar projections, producing a relatively selective loss of lateral spinal input to motoneurons innervating muscles of the arm. Since there is usually no direct interruption of reticular and vestibular systems at the brainstem, descending spinal projections from these systems would be preserved or perhaps even enhanced. The observed EMG patterns could reflect motor acts controlled by these ventromedial pathways, such as postural or attitudinal responses (*see* Beevor, 1904; Twitchell, 1951).

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HEMISPHERE ASYMMETRY FOR EYE GAZE MECHANISMS

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SUMMARY

To investigate left/right asymmetries in cerebral gaze mechanisms, eye deviation was evaluated in 90 patients following intracarotid sodium amylobarbitone injections. For right-handed subjects with left cerebral language dominance, the occurrence and severity of eye deviation were greater for right versus left hemisphere injections. In contrast, subjects with mixed cerebral dominance for language/handedness exhibited no left/right difference in the incidence of eye deviation. The results are consistent with right cerebral dominance for attentional/intentional mechanisms directed at external space. Further analysis suggests that the cerebral asymmetry for gaze may be due to an evolutionary loss of attentional/intentional mechanisms by the left cerebral hemisphere as language function developed.

INTRODUCTION

Although the oculomotor system encompasses a distributed network whose intrinsic organization is one of the most complex of neural subsystems, the relationship between unilateral cerebral lesions and conjugate lateral gaze has been well demonstrated through a variety of investigations employing clinicopathological correlations and stimulation and/or lesioning techniques (Bizzi *et al.*, 1971; Bender, 1980). When the effects of the two cerebral hemispheres are equally balanced, the eyes and head are directed straight ahead. Voluntary activation or electrical stimulation of one cerebral hemisphere produces turning of the eyes and head towards contralateral hemispace. Conversely, a lesion of one cerebral hemisphere typically produces eye and head turning toward ipsilateral hemispace. Since the effects of the two cerebral hemispheres are balanced when the eyes are in the primary position, the ipsilateral conjugate gaze deviation associated with unilateral cerebral hemisphere lesions reflects a deficit in the ipsilateral supranuclear

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gaze mechanisms. This phenomenon was initially reported by Andral (1834) and first investigated systematically by Prevost (1868). The clinicopathological study of 51 patients by Prevost remains the largest autopsy-verified series. In addition, he confirmed his clinical observations with animal experiments that employed lesioning by direct cerebral trauma or by intracarotid injections of emulsified tobacco.

Despite numerous subsequent investigations, a left/right cerebral asymmetry for gaze mechanisms was not noted until 1982 when De Renzi *et al.* (1982) reported that gaze paresis was more frequent (72/120), severe and persistent in patients with right cerebral lesions. They postulated that the left/right gaze differences were due to an asymmetric anatomical distribution of the oculomotor system in the two hemispheres, with the system represented more diffusely on the left and more focally on the right. However, these conclusions were based on clinical data, and the majority of cases had neither radiological nor pathological verification of lesion distribution. Mohr *et al.* (1984) also reported a right cerebral predominance for gaze paresis in 531 cases of hemisphere stroke, but an asymmetric left/right distribution of deep lesions precluded firm conclusions concerning left/right hemisphere mechanisms.

Accumulating evidence suggests a specialized role for the right hemisphere in attentional and intentional mechanisms directed toward external space (Heilman and Valenstein, 1979; Mesulam, 1981; Heilman *et al.*, 1985*a*). Intentional mechanisms refer to the neural systems which prepare and direct motor responses. Electrophysiological and positron emission tomographic studies have demonstrated that the right cerebral hemisphere exhibits greater activation than the left during tasks requiring direct sensory attention (Desmedt, 1977; Heilman and Van Den Abell, 1980; Reivich *et al.*, 1983). In addition, while the left cerebral hemisphere attends primarily to right hemispace, the right cerebral hemisphere attends to both sides (Heilman and Van Den Abell, 1980; Reivich *et al.*, 1983; Weintraub and Mesulam, 1987). A similar right brain advantage has been shown in reaction time studies (Heilman and Van Den Abell, 1979). Finally, hemi-inattention, hemispatial neglect and hypokinesia appear to be more common following right than left cerebral lesions (Costa *et al.*, 1969; De Renzi *et al.*, 1970; Faglioni *et al.*, 1971; Gainotti *et al.*, 1972: Albert, 1973; Oxbury *et al.*, 1974; Colombo *et al.*, 1976; Denes *et al.*, 1982; Heilman *et al.*, 1985*b*). Based on these data, we present an alternative hypothesis to the anatomical postulate of De Renzi. We propose that a functional asymmetry for attentional/intentional systems exists such that the right cerebral hemisphere may direct the eyes towards either hemispace, while the left cerebral hemisphere is limited in its capacity to direct the eyes ipsilaterally.

In the present study, we investigated prospectively the left/right incidence of gaze paresis during the intracarotid sodium amytal (ISA or Wada) procedure (Wada, 1949; Branch *et al.*, 1964). A short acting barbiturate, sodium amylobarbitone, was injected sequentially into each internal carotid artery to anaesthetize transiently the left and right cerebral hemispheres independently. This technique is employed clinically to determine cerebral dominance for language. For the present study, ISA offers the advantage of matching left and right brain lesions while studying the effects of transient cerebral dysfunction in each hemisphere of each individual. If De Renzi's hypothesis of anatomical distribution is correct, then there should be no difference in gaze paresis between the right and left ISA injections. However, if our functional postulate is correct, there should be an asymmetry of gaze paralysis.

METHODS

Ninety patients with intractable epilepsy underwent the ISA procedure as part of their preoperative evaluation for epilepsy surgery. Demographic data are depicted in Table 1. Handedness was determined by the Benton Handedness Inventory (Benton *et al.*, 1962). Seizure focus was determined by multiple scalp, sphenoidal, and/or intracerebral electroencephalographic ictal recordings. Injections were administered via a catheter following a transfemoral approach. ISA dosages were determined on an individual basis. All patients received incremental injections of sodium amytal (initial dosage 50–75 mg, 25 mg increments) necessary to produce a contralateral flaccid hemiplegia. Mean left hemisphere dosage was 106 mg (SD 42.1) and mean right hemisphere dosage 101 mg (SD 36 6). Injections were administered by hand over a 4 s interval, and the order of injection was alternated sequentially. Left and right ISAs and arteriograms were performed on the same day. Patients were retested before the second injection to ensure return to baseline. All sessions were videotaped.

TABLE 1 SUBJECT DEMOGRAPHICS

Mean age: 30 (13–61) yrs
Sex: 49 M, 41 F
Handedness· 82 R, 7 L, 1 A
Language dominance: 75 L, 15 mixed
Seizure focus: 33 L, 32 R, 9 bilateral, 7 diffuse, 9 unknown

Patients were tested in the supine position. The primary examiner stood directly above the head of the angiography table. Assistants stood to the left and right of the table At the start of the test, the patient held his arms straight up with the hands supinated and fingers extended. He/she was instructed to look straight ahead and count repeatedly from 1 to 20. The ISA injection was then administered. At the onset of flaccid hemiplegia, patients were instructed to stop counting if speech arrest had not occurred. Observations were then made for the presence of spontaneous, tonic (i.e., $\geqslant 2$ s) eye deviations from the midline. Examiners to the left and right of the angiography table called for the patient to look towards the contralateral and then the ipsilateral side. (Patients were instructed before the ISA injection in the procedure of looking to the left and right on command.) Next, the response to a simple command (i.e , touch your nose) was assessed. Real objects and abstract figures were presented for subsequent postrecovery recall. Evaluation then continued with tests of language, spatial abilities, strength and sensation during the duration of ISA effect. Cerebral dominance for propositional language was determined based on speech arrest, comprehension, repetition and naming.

The second half of the series (i.e., 45 patients) was also rated (0–3) for severity of eye deviation. The severity ratings were made according to the following scale: 0 = no deviation; 1 = transient eye deviation of less than 10 s (without head deviation); 2 = eye deviation of 10–30 s duration (±head deviation); 3 = sustained eye deviation greater than 30 s (usually with associated head deviation). Final ratings required the agreement of the 3 observers. Any disagreements were reviewed on videotape to reach a unanimous rating.

Arteriograms were obtained and subsequently evaluated for crossflow by a neuroradiologist blinded to the ISA results. Arteriograms were performed using Medrod Mark IV pressured injections into the intracarotid arteries via a catheter following a transfemoral approach. Even though mechanical pressured injections are more likely to produce crossflow than the slower low pressure hand injections used for the ISA procedure, arteriograms were analysed for severity of crossflow in order to exclude any contribution of crossflow to the observed left/right differences in gaze paresis. Arteriograms were rated (0–3) for the presence and persistence of crossflow in the anterior, middle and posterior cerebral artery distributions.

RESULTS

When gaze deviation occurred, the eyes moved conjugately towards the ipsilateral side in almost every case. The deviation was tonic and associated with the development of hemiplegia. Following left ISA, patients usually did not respond to command and exhibited few spontaneous saccades immediately postinjection. Following right ISA, patients were able to perform pursuit and saccade manoeuvres on command but were frequently unable to direct gaze volitionally past the midline. Since aphasia interfered with testing of eye movements to command following left ISA, we chose to limit our analysis to the left/right ISA difference in spontaneous tonic eye deviation.

TABLE 2 EYE GAZE AFTER ISA INJECTION (n = 90)

Injection	*Left*	*Mid*	*Right*
Left	29	58	3
Right	1	35	54

The raw data are presented in the figure and Tables. After left ISA, 32% of the patients exhibited ipsilateral gaze deviation and 100% exhibited some language dysfunction. After right ISA, 60% had gaze deviation and 17% had language deficits. In the group with greatest cerebral lateralization (i.e., dextrals with left language dominance), 26% exhibited ipsilateral eye deviation after left ISA and 61% after right ISA. In the group with mixed cerebral dominance, 55% exhibited ipsilateral gaze deviation after left ISA and 55% after right ISA.

A sign test was run on the 49 patients who exhibited a gaze paresis after one injection but not the other. Gaze paresis was more frequent after the right injection ($P \leqslant 0.0002$). This effect was even more marked ($P \leqslant 0.00006$) when the analysis was limited to dextrals with left language dominance. Cerebral lateralization significantly affected ISA gaze results (χ^2 (3) = 7.66, $P \leqslant 0.05$). In fact, subjects with mixed cerebral dominance for handedness and/or language exhibited no difference in the incidence of eye gaze deviation following left and right ISA injections.

TABLE 3 EYE GLAZE RELATED TO CEREBRAL DOMINANCE

Eye gaze in dextrals with left language dominance ($n = 70$)

Injection	*Left*	*Mid*	*Right*
Left	18	49	3
Right	1	26	43

Eye gaze in patients with mixed dominance ($n = 20$)

Injection	*Left*	*Mid*	*Right*
Left	11	9	0
Right	0	9	11

A sign test was also run on the subset of 45 patients with severity scores. Gaze paresis was significantly more severe after right versus left ISA injections ($P \leqslant 0.001$). In addition, the magnitude of change in severity between the left and right injections was larger towards the right. As reflected in the rating scores, the duration of deviation was longer after right ISA. In some cases (almost always after right ISA), the duration of the eye deviation was prolonged for several minutes (e.g., the longest duration was greater than 9 min). In these patients, the deviation required presentation of test stimuli in the extreme right visual field.

χ^2 analyses failed to reveal any effects on gaze paresis for side of seizure focus (χ^2 (4) = 2.94, n.s.), order of injection (χ^2 (4) = 2.00, n.s.), dosage (left ISA: χ^2 = 4.32, n.s.; right ISA: χ^2 (6) = 4.81, n.s.) or sex (χ^2 (4) = 0.76, n.s.). The Wilcoxon matched-pairs signed-ranks test was used to analyse for left/right differences in crossflow on cerebral angiography. No significant left/right differences were found for anterior ($z = 1.09$, $P \leqslant 0.28$, n.s.), middle ($z = 0.23$, $P \leqslant 0.82$, n.s.), posterior ($z = 0.13$, $P \leqslant 0.90$, n.s.) or total hemisphere circulation ($z = 1.20$, $P \leqslant 0.23$, n.s.).

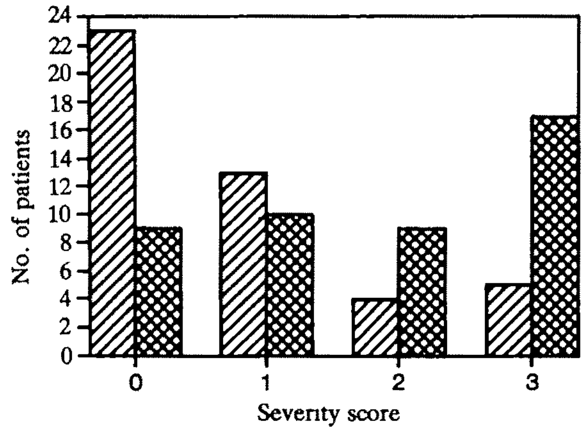

FIG. Bar graph showing distribution of severity scores for gaze paresis following ISA injections in 45 subjects. Gaze deviation is rated as: none = 0, mild = 1, moderate = 2, severe = 3. Single cross-hatching = left gaze after left ISA; double cross-hatching = right gaze after right ISA. Note greater severity of gaze deviation following right ISA.

DISCUSSION

A left/right brain asymmetry in gaze mechanisms is demonstrated with the incidence and severity of gaze paresis being greater for right cerebral dysfunction. The results cannot be explained by side of seizure focus or the effects of crossflow. The findings support a hypothesis of a functional asymmetry in gaze mechanisms between the left and right brain. As noted previously, the ipsilateral conjugate eye deviation associated with unilateral cerebral hemisphere dysfunction reflects an input deficit of the ipsilateral supranuclear gaze mechanisms to the control of gaze direction. To some extent, the intact cerebral hemisphere can direct gaze in both directions as evidenced by the preservation of horizontal saccades following unilateral cerebral lesions (Lesser *et al.*, 1985). In the present study, input from the intact left cerebral hemisphere did not overcome the effects of right ISA on gaze as well as the intact right brain compensated during left ISA. It therefore appears that the right brain has a greater capacity to direct the eyes towards either hemispace than the left brain which appears limited in its ability to direct the eyes ipsilaterally. Although eye gaze is largely a motor phenomenon and reflects mainly intentional mechanisms, we have also found a similar left/right ISA asymmetry for tactile extinction (Meador *et al.*, 1988). Further, attentional and intentional mechanisms are separable but function interactively (Goldberg and Segraves, 1987). We therefore postulate that the gaze asymmetry is due to right cerebral dominance for attentional/intentional mechanisms directed at external space.

The present experiment was conducted during a clinical study whose primary function is to assess lateralization of language. Thus the ISA procedure is routinely performed with the patient initially counting. Could the verbal task influence gaze orientation (Kinsbourne, 1972)? The effect of a verbal task on gaze orientation is subtle and may be abolished if subjects are asked to hold central fixation, or if they are confronted by the experimenter or his voice (Kinsbourne, 1974). In the present study, the verbal task may have initially facilitated eye deviation, but this influence cannot explain the persistence of the deviation after cessation of counting (when our observations were made) and during nonverbal tasks. Further, it does not explain the severe longer lasting gaze paresis seen after right ISA, in which patients could not gaze left past the midline on command.

The difference in gaze paresis between the group with greatest cerebral lateralization (i.e., dextrals with left cerebral language) and those with mixed cerebral dominance, is noteworthy. The cerebral asymmetry for gaze paresis was present only for dextrals with left language dominance, suggesting a relationship of cerebral lateralization to gaze mechanisms. Hemisphere asymmetry of complex behavioural functions is a fundamental aspect of human cerebral evolution (Mesulam, 1985). The left hemisphere is specialized for language and praxis, while the right hemisphere is specialized for complex visuospatial perceptual tasks, some aspects of emotional behaviour and the spatial distribution of attention and intention (Heilman and Valenstein, 1985). At least two hypotheses concerning the development of the right hemisphere specializations are possible (Mesulam, 1985). According to the first, the specialized nonlinguistic functions of the right brain were initially equally distributed between the two hemispheres, but during subsequent development of language, the left brain's nonlinguistic abilities were reduced. Thus the right brain specializations appeared secondary to the reduced capacity of the left. Since the left brain retains some of its prior functions, this hypothesis predicts that left brain lesions would disrupt nonlinguistic functions to a greater degree than equivalent lesions of the right brain would impair language. According to the alternative hypothesis, the right brain specializations represent emergent functions which evolved simultaneously with left cerebral language. This hypothesis predicts that left brain lesions would disrupt nonlinguistic functions to approximately the same degree that right brain lesions impair language.

Evidence to resolve the two hypotheses has been lacking because of difficulties in matching left/right lesions and in avoiding covert linguistic mediation of the 'right brain' task (Mesulam, 1985). The present study addresses these issues and allows a direct comparison of linguistic and intentional deficits. Left ISA produced gaze deviations more frequently than right ISA produced language deficits. This effect was more pronounced in the group with greatest cerebral lateralization (i.e., dextrals with left language dominance). Further, the occurrence of gaze deviation after either left or right ISA in subjects with mixed cerebral dominance is comparable to the occurrence after right but not left ISA in dextral subjects with left cerebral language dominance.

The results suggest that the role of the left brain in directed spatial attention/intention diminished as it evolved language specialization. Thus eye gaze asymmetry in the present study appears to be secondary to the left brain's reduced capacity to direct the eyes ipsilaterally. Whether more complex nonlinguistic functions of the right brain developed by a similar process or by emergent evolution is uncertain.

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IMPAIRMENT AND RECOVERY OF IPSILATERAL SENSORY-MOTOR FUNCTION FOLLOWING UNILATERAL CEREBRAL INFARCTION

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SUMMARY

After unilateral cerebral hemisphere stroke, resulting in contralateral arm symptoms but largely sparing higher cerebral function, ipsilateral arm function is generally considered to be unaffected. In this study, 8 subjects with acute unilateral cerebral infarction (confirmed by CT scan) and primarily motor deficits underwent 11 computerized and 6 clinical assessments between 11 days and 12 months poststroke, and were compared with 12 normal subjects. Computerized tests comprised 3 pursuit tracking tasks (preview-random, step and a combination of these), designed to measure different aspects of integrated sensory-motor (S-M) function, and 12 tasks aimed at breaking tracking into various sensory, perceptual and motor components (joint movement sense, visual resolution, object perception, static and dynamic visuospatial perception, range of movement, grip and arm strength, reaction time, speed, static and dynamic steadiness).

The asymptomatic arm was impaired on all but one of the computerized tests throughout the 12-month period, although to a lesser degree than the symptomatic arm. Grip strength was marginally impaired initially. Incomplete neurological recovery was seen in the asymptomatic arm for all functions except strength, speed and steadiness, possibly indicating their resistance to improvement. Clinical assessment detected no asymptomatic arm impairment and only a mild transient deficit of higher mental function.

Our data suggest that (1) all cerebral hemisphere areas involved in S-M functions can exert some degree of bilateral motor control; (2) ipsilateral influence is never greater than contralateral influence, and is usually considerably less; and (3) the proportion of ipsilateral to contralateral control is closely related to the degree of continuous sensory feedback required by the particular task. The mechanism and degree of ipsilateral dysfunction can be explained by a 3-tier cerebral model of S-M integration comprising a lower level of functions with high contralateral specificity (somatosensory and motor), a middle level of non-limb-specific partially lateralized functions (ideomotor praxis and visuospatial perception) and an upper level of global mental activities (intellect, alertness, etc.).

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INTRODUCTION

It is commonly believed that unilateral cerebral hemisphere stroke, resulting in contralateral arm weakness (with or without associated impairment of somatic sensation) but sparing higher cerebral function, does not cause ipsilateral arm dysfunction. There is evidence that this is not correct.

Most studies of ipsilateral limb function in man have used standard psychological tests, particularly those based on the Halstaed-Reitan Neuropsychological Test Battery (Reitan and Davison, 1974). Cerebral lesions investigated have been vascular, neoplastic or traumatic, and have been unilateral as far as could be determined.

Ipsilateral (as well as contralateral) deficits have been demonstrated from lesions in either hemisphere on skilled sensory-motor (S-M) tasks such as pegboard (Vaughan and Costa, 1962; Wyke, 1971; Haaland and Delaney, 1981), static and movement (vertical groove) steadiness (Haaland and Delaney, 1981), maze coordination (Haaland and Delaney, 1981), pursuit rotor (Heap and Wyke, 1972) and on various somatic sensation/perceptual tests (Semmes *et al.*, 1960; Vaughan and Costa, 1962; Boll, 1974). There are two reports of S-M functions being impaired bilaterally from lesions in one but not the other hemisphere. The first is impaired finger tapping from left lesions (Wyke, 1971). We dispute this, however, as analysis of her data indicates significant ($P < 0.05$, one-tail) impairment of tapping with right lesions as well. In addition, Wyke's results conflict with those of Carmon (1971) and Dodrill (1978) who found, and Haaland and Delaney (1981) who did not find, significant ipsilateral impairment of tapping speed with right and left lesions. The second is impaired maze coordination and grooved pegboard performance from left lesions (Haaland *et al.*, 1977). However, subsequent analysis (Haaland and Delaney, 1981), which took account of pronounced heterogeneity of variance across groups, found no difference between the right and left hemisphere groups.

Grip strength is the only S-M function for which no ipsilateral deficit has generally been found (Kimura, 1977; Haaland and Delaney, 1981). Possible exceptions are Dodrill (1978), Finlayson and Reitan (1980) and Hom and Reitan (1982). In Dodrill's brain-damaged subjects, however, the lesions were not necessarily unilateral and in the latter papers the statistical significance of the differences is not stated.

In addition to demonstrating an ipsilateral (and contralateral) component to many S-M functions, several authors have shown significant predominance of certain functions in one or other hemisphere, although such studies have often been contradictory. Greater left hemisphere bilateral control (i.e., left lesions producing greater deficits in both arms than right lesions) has been shown for a wide variety of S-M tests including somatic sensation (Semmes *et al.*, 1960; Vaughan and Costa, 1962), tapping speed (Wyke, 1971), manual sequence (Kimura, 1977), and eye-arm precision, such as on Purdue pegboard (Vaughan and Costa, 1962). Conversely, greater right hemisphere bilateral control has been demonstrated on tactile-perceptual tests (Boll, 1974) and on a wide range of S-M tests from the Halstaed-Reitan battery (Hom and Reitan, 1982), although results of individual tests from the latter were not reported.

As part of a larger study to quantify impairment and recovery of upper limb S-M function following unilateral cerebral infarction, we investigated a wide range of S-M functions in the arm ipsilateral to the cerebral lesion, in patients without major nonmotor (other than possible sensory) deficits. Emphasis was on proximal rather than distal arm function. The development of a battery of 15 computerized tests to measure various aspects of S-M function, especially following brain damage (Jones and Donaldson, 1981, 1986; Jones, 1987), was central to this study.

METHODS

Subjects

Patients were selected from acute stroke admissions to Christchurch hospitals, screening being performed by a neurologist (*see* Table 3). In addition, selective neuropsychological tests were administered (WAIS Picture Completion, Benton Visual Retention, Reading/Demographic and Digit Span), these chosen as representative of the visuospatial and information processing skills employed in performing the S-M tasks used in this study. Patients who proved to have other than mild deficits of higher mental function were excluded.

Eleven patients initially fulfilled the following criteria: (1) unilateral cerebral infarction, (2) CT scan excluding pathologies other than unilateral cerebral hemisphere infarction, (3) symptomatically impaired upper limb function, (4) other than possible somatic sensory impairment, no major nonmotor deficit (i.e., visual, auditory, perceptual, praxic, language, memory, alertness and intellect), (5) premorbid right-handedness, (6) ability to attend over a 12-month assessment period and (7) informed consent. Two patients withdrew at an early stage and a third was excluded by a second major stroke.

The 8 stroke subjects who completed the study are outlined in Table 1. Patients fell into two broad categories: mild to moderate upper limb weakness (n = 5) and severe upper limb weakness (n = 3). One densely hemiplegic subject (Case 8) had a degree of constructional dyspraxia. Corrected

TABLE 1. STROKE GROUP (ACUTE UNILATERAL CEREBRAL INFARCTION)

			CT scan (infarct)				
Case	*Sex*	*Age (yrs)*	*Site*	*Diameter (approx.)*	*S-arm*	*Paresis (S-arm)*	*Sensory deficit (S-arm)*
1	M	68	R external capsule + BG	1 cm	L	Mild	Nil
2	F	76	L frontoparietal (cortical + subcortical)	4 cm	R	Mild	Mild
3	F	61	Normal (presumed L subcortical lacune)	—	R	Moderate	Nil
4	M	61	R temporoparietal (cortical + subcortical, IC spared)	4 cm	L	Mild	Severe
5	F	73	L frontoparietal (subcortical)	1 cm	R	Mild	Nil
6	M	57	R frontal (subcortical) + IC + BG	3 cm	L	Severe	Moderate
7	M	62	R frontotemporal (subcortical) + IC + BG	4 cm	L	Severe	Severe
8	M	53	R frontotemporal (subcortical) + IC + BG	4 cm	L	Severe	Severe

IC = internal capsule, BG = basal ganglia; S-arm = symptomatic arm; R = right; L = left.

visual acuity was 6/9 or better in one eye (only one patient was not 6/6 or better with both eyes together) and no patient had a field defect or diplopia.

There were two normal control groups, corresponding to single and multiple sessions on the test battery. The single session group contained 36 subjects divided evenly into sex, and six age subgroups, with a subset of 12 of these making up the second group who undertook a further 10 test sessions. All subjects were right handed, had corrected visual acuity of 6/9 or better in one eye and were drawn from a wide range of employments and backgrounds.

TABLE 2 STROKE, STROKE-MATCHED NORMAL (1 SESSION) AND MULTIPLE SESSION NORMAL GROUPS

		Normal	
	Stroke	*Stroke-matched** *(1 session)*	*Multiple session* *(11 sessions)*
n	8	8	12
Age (yrs)			
Mean	63.9	63.5	44.7
SD	7.9	8.2	18.2
Range	53-76	47-72	22-72
Male:female	5:3	5:3	6:6
Driving licence	5	5	11

* Four subjects in the stroke-matched normal group were also in the multiple session normal group

Most analyses of our data involve comparison of the patient group with the multiple session normal group. As indicated in Table 2, the composition of these two groups differ in age, sex and driving status (i.e., licence holder). To evaluate whether these factors might account for differences in performance, a subgroup of 8 of the 36 subjects in the single session group was formed to match as closely as possible these factors in the stroke group (Table 2). This could then be compared with the stroke and multiple session normal groups (although only on first session) to establish whether these biographical differences had any influence on performance. The resultant stroke-matched normal group and the stroke group were nearly identical in mean age, sex, dominance and driving status, although match was not done on a paired subject basis.

Apparatus and tests

Quantitative and clinical assessments were applied serially and in parallel during the study.

Quantitative S-M test battery assessment (QSMB)

System hardware was based around a PDP-11/34 computer with a VT11 graphics screen (279 mm × 228 mm) for displaying test stimuli (eye-screen distance 132 cm). A steering wheel (395 mm diameter, and minimal 1.0 N friction at perimeter) was used to measure the subject's motor output except for grip strength. S-M integrated and component tests (*see* below and fig. 1) were generated and analysed by two programs (TRACK and SMC, respectively), each of which ran within 64 kbytes of memory under the RT11 operating system. Software was written in FORTRAN IV, except for display of moving stimuli in the dynamic perception task and three tracking tasks, for which the faster MACRO assembly language was necessary.

Integrated function tests. As details are given elsewhere (Jones and Donaldson, 1986), only a summary of the 3 tracking tasks is provided. Each task lasted 120 s and subjects were instructed to maintain an arrow point on the input target signal throughout the test. Rotation of the wheel moved the arrow horizontally.

1 Random tracking task (preview). The input target signal was a random waveform of 0.21 Hz bandwidth. This descended from the top of the screen giving an 8.0 s preview time before reaching the point of an arrow. The task required smooth movements over a 175° range of the steering wheel. Of several performance parameters obtained, the mean absolute error is the only one presented in this study.

2. Step tracking task (nonpreview) This task comprised 32 abrupt steps alternating between displacement from and return to centre screen. Spatial unpredictability was present in the outward steps through four randomly distributed amplitude/direction movements: large steps (90° on wheel) and small steps (22.5° on wheel), both to right and left of centre. Four randomly distributed durations between steps (2 8, 3.4, 4.0, 4.6 s) and lack of preview ensured temporal unpredictability. Stimulus unpredictability and ballistic response place the step task at the opposite end of the S-M spectrum to the random task. Mean absolute error is again the only score presented in this study.

3. Combination tracking task. In combination tracking the stimulus alternately cycled between the random and step tracking modes over 11 s cycles Thus, while tracking the random input, the preview signal was abruptly and unpredictably replaced by a stationary vertical line at a distance horizontally displaced from the random tracking signal. The reverse applied at the end of the step tracking mode with the reappearance of the random tracking random signal at another place on the screen. Combination tracking allows determination of the effect of repeated translation between different tracking modes on performance.

Component function tests. Each component function test was designed to isolate and quantify various elements of integrated function measured during tracking. Consequently, there was close resemblance between the component and integrated function tests and validity of comparisons between them was maximized. In those tests allowing several attempts, best rather than average scores were used as best score is considered a more accurate measure of maximal ability by minimizing the effect of inconsistency. Tests moved progressively through visual (sensory/perceptual), proprioceptive and motor component functions.

1. Visual acuity. Corrected visual acuity for each eye measured on the Snellen chart at 6 m.

2. Visual resolution. Visual resolution was measured by ability to identify the position of a dot with respect to a vertical line on the graphics screen. Dot-line separations were in multiples of 0.27 mm.

3. Arrow perception. Perception and comprehension of the components of an arrow identical to that used in tracking tasks with particular emphasis on arrow point.

4. Static perception. Perception of position of the arrow point with respect to a static vertical line in 4 trials and a static sinewave in 16 trials.

5. Dynamic perception. Determination of whether an arrow point stayed perfectly on a random input descending the screen with 8 s preview time. The duration of 20 trials decreased from 10 to 2 s and various error offsets were simulated.

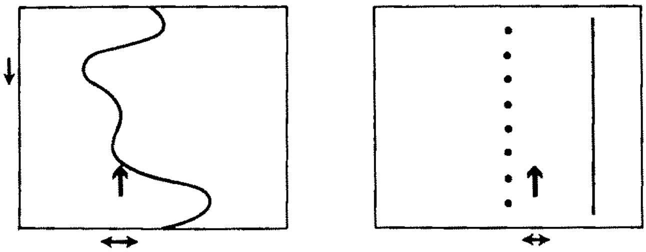
6 Joint movement sense. Determination of the direction of small manually applied and mechanically limited movements to the rim of a steering wheel while the subject was blindfolded, with his hand grasping the top of the wheel Displacement stimuli ranged from 32.0 mm down to 0.5 mm.

7. Grip strength. Best of three attempts on a TEC dynamometer with the arm extended from the side.

8. Range of movement. Comfortable active range of movement on a steering wheel while maintaining a firm grip.

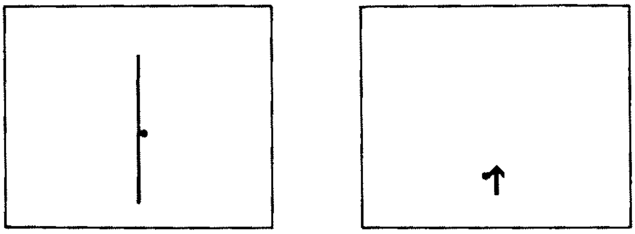
9. Arm strength. Average of greatest force achieved on 2 attempts at each of 4 hand position-direction conditions on a steering wheel (0° to right, 0° to left, +90° to left, −90° to right; where 0° is the top of the wheel when the arrow is centre screen).

10 Ballistic movement. Fastest possible arm movement in response to a random nontarget stimulus



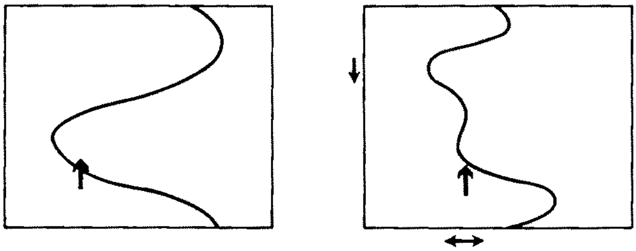
Random tracking (preview): keep point of arrow on or as close to descending random waveform

Step tracking (nonpreview): keep point of arrow on jumping line; place emphasis on both speed and accuracy



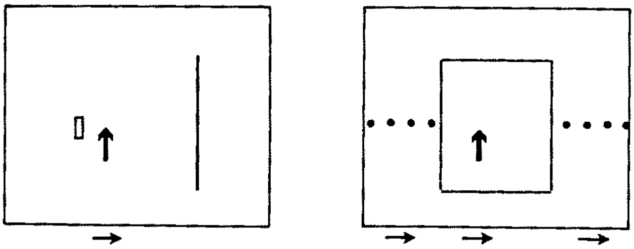
Visual resolution: determine whether dot is to the left of, right of, or on vertical line

Arrow perception: determine whether flashing dot is on point of arrow or not (3 on, 10 off)



Static perception: determine whether point of arrow is to the left of, right of, or on static waveform (5 on, 15 off)

Dynamic perception. determine whether point of arrow stays on descending random input (6 on, 14 off)



Ballistic movement: move arrow out of box and across line as fast as possible when dotted line goes solid (gives reaction time and speed)

Steady movement: move arrow through box region as smoothly as possible at a speed similar to pacing dots

FIG. 1 Further description of some of QSMB tests.

(no accuracy required). This required moving the arrow out of a box and across a pass-line equivalent to 90° of movement on a steering wheel in response to a random 3–7 s latency stimulus. The best reaction time and speed over 8 attempts were recorded.

11. Static steadiness. Steadiness with the arm extended and the hand grasping a steering wheel at +90° or −90° (= maximum gravity positions) and measured as average deviation of velocity from zero over 7 s duration.

12. Steady movement. Steadiness of attempted constant-speed nonpursuit movement on the steering wheel over a range of 116°. The best of 8 attempts within speed range of 17.7 to 34.7°/s was recorded.

Clinical S-M examination

Comparison of QSMB with conventional neurological examination was important in determining the former's sensitivity, reliability and validity. Published ordinal neurological evaluations were considered unsuitable and a standardized 'Clinical examination of upper limb S-M system' was designed (Table 3). Neurological signs and functions in the examination are in the categories of: higher mental functions, range of limb movement, painful movement, involuntary movement, strength, tone, coordination, reflexes and somatic sensation. Items were rated on a 4-level ordinal impairment scale except for strength and coordination categories in which intermediate values, and hence 7-level items, were considered appropriate. Conversely, only a 'normal' or 'abnormal' 2-level score was meaningful for sensory inattention.

Two aggregate scores were derived for each arm from clinical examination. (1) Clinical Deficit (CD). CD is the sum of all scores per arm (including nonlateralized function) with unity weightings. This cumulative index includes diagnostic signs which may have no direct functional implication. (2) Functional Deficit (FD). FD is the sum of all functionally weighted scores per arm. Weighting factors were empirically assigned according to perceived importance of items to general upper-limb performance, that is, on a wide range of unspecified eye-arm tasks.

Procedure

The stroke and multiple session groups underwent 11 sessions over 1 yr. Spacing was approximately exponential with patients starting on the eleventh day poststroke. Clinical and component tests were applied on alternate sessions. Subjects started tests on the first session with their 'preferred arm'. For all normal subjects this was their right arm whereas for patients it was their asymptomatic arm. The starting arm was alternated in subsequent sessions. All clinical examinations were carried out by one neurologist and without reference to previous test scores.

Analysis

Statistical analysis was by BMDP Statistical Software (Dixon, 1981). Nonparametric statistics have been applied throughout because several variables are inherently nonquantitative (e.g., clinical S-M examination, visuoperceptual tests) and many quantitative variables have skewed distributions as well as different variances between normal and patient groups.

Two sources of confounding bias. If present, impairment in the stroke group should be at its lowest level and most difficult to demonstrate in the asymptomatic arm at 12 months. Hence it will also be the most vulnerable to any confounding effect from nonmatching between subject groups or in experimental design. Apart from the stroke, there were two important differences between stroke and multiple session control groups which could be responsible for small differences in performance.

1. Nonmatching of age, sex and driving status. Multiple session normal subjects were in part optimally chosen for study of the effects of age and sex on normal performance (Jones *et al.*, 1986). This, together with random presentation of suitable stroke patients, meant that the two groups differed in age, sex and driving status (Table 2).

2. Nonmatching of starting-hand. As outlined above, all subjects started tests on the first session

TABLE 3 CLINICAL EXAMINATION OF UPPER LIMB SENSORY-MOTOR SYSTEM

Higher mental function[a]
Alertness (2)*
Orientation (2)*
Intellect (2)
Motivation (2)*
Cooperation (2)*
Emotional stability (2)*
Language comprehension (2)*
R/L discrimination (2)
Visuospatial orientation (2)*
Praxis—constructional (2)
Visual inattention (2)

_Range of movement_*
Shoulder (1)*
Elbow (1)*
Forearm (1)*
Wrist (1)*
Digits (1)*

_Painful movement_*
Shoulder (1)*
Elbow (1)*
Forearm (1)*
Wrist (1)*
Digits (1)*

_Involuntary movement_*
Tremor (3)*
Other (3)*

Hypertonia
Shoulder (1)
Elbow (1)
Forearm (1)
Wrist (1)

Muscle weakness[b]
Shoulder—flexion (1)
—extension (1)
—abduction (1)
—adduction (1)
Elbow—flexion (1)
—extension (1)
Forearm—pronation (1)
—supination (1)
Wrist—flexion (1)
—extension
Digits—flexion (1)
—extension (1)
—abduction (1)
—adduction (1)

Coordination[b,c]
Rapid alternating movement (3)
Finger-nose-finger (3)
Finger agility (3)

Reflexes (increased or reduced)
Biceps (0)
Triceps (0)
Supinator (0)
Finger (0)

Somatic sensation
Touch (3)
Pain (0)
Vibration (0)
Position (3)
2-point discrimination (0)
Sensory inattention (3)

All items rated on a 4-point ordinal impairment scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe) giving maximum unweighted score of '3' for all items, except sensory inattention which is '1'. Clinical deficit = CD = sum of unweighted scores (per arm). Functional deficit = FD = sum of weighted scores (per arm). FD weightings are in parentheses after each item.

[a] Scores of nonlateralized functions added to scores of both arms. [b] Intermediate levels permitted (7-point ordinal scale). [c] Items untestable due to weakness (e.g., coordination) were given maximum impairment score of '3'. * Items had '0' (normal) score for all subjects.

with their 'preferred arm'. Thus although all patients were premorbidly right handed, 3 started with their left arm. As the limb tested second benefits by the experience of the first, functions for which the dominant right arm is normally superior are inherently disadvantaged in the asymtomatic arm of the stroke group, and advantaged in the symptomatic arm, with respect to the normal subject group. It might be considered that this confounding effect could be eliminated by always comparing right with right, and left with left, but this would introduce a more serious practice order effect. Another possibility might have been for patients to start with right arm irrespective of paresis. This

TABLE 4 INFERIORITY BIASES OF STROKE GROUP WITH RESPECT TO MULTIPLE SESSION NORMAL GROUP

	Inferiority biases[a]		
Test	*Age/sex/ driving*[b]	*Starting hand*[c]	*Total*
Grip strength (kg)	−2.0	0.7	−1.3
Arm strength (N)	−6.5	1.9	−4.6
Reaction time (ms)	−3.1	−1.6	−4.7
Speed (deg/s)	80	10	90
Steadiness (mdeg/s)	30	2	32
Steady movement (deg/s)	−0.08	0.01	−0.07
Random (bit)	3.34	−0.06	3.28
Step (bit)	1.34	−0.03	1.31
Combination (bit)	2.55	0.93	3.48

[a] Inferiority biases are positive if the stroke group was determined to be premorbidly inferior to multiple session normal group, irrespective of whether function is measured as performance or error Biases are in absolute units of the test functions.

[b] Age/sex/driving status biases for component functions (grip strength, arm strength, reaction time, speed, steadiness, steady movement) are equal to absolute difference between multiple session and stroke-matched normal groups on session 1. The same biases for integrated functions (Random, Step, Combination) are equal to the same differences but reduced in proportion to decreases in error scores of multiple session normal group over the 12-month trial. This reduced bias takes into account greater independence of percentage than absolute performance increments from performance level (Jones, 1987) (*see also* Jones and Donaldson (1981) for illustration of decrease in effect of age on tracking with subsequent sessions)

[c] Starting-hand inferiority bias for asymptomatic arm = 0.375 × R/L differential, where 'R/L differential' is the trial average absolute differential between right and left arms for multiple session normal group (differential is positive if R is superior to L) and '0.375' corresponds to 3 of 8 stroke subjects who chose their premorbid nondominant left arm to be the 'preferred' starting arm.

would unfairly disadvantage patients with severe right-sided paresis, whose left arm would receive little or no benefit from the prior experience of the right.

Adjustments to motor test scores of stroke patients were made to offset artificially the two sources of nonmatching bias. The biases and their derivation are given in Table 4.

RESULTS

Impairment

Both raw and 'match-adjusted' ipsilateral deficits of the stroke group at 11 days and 12 months poststroke are given in Table 5. Raw scores for the contralateral arm are presented to illustrate the much greater deficits in that limb.

Static and dynamic perception were impaired in the stroke group at 11 days, even although visual resolution was superior to that of the normal group. Arrow perception was not impaired, which may reflect the simplicity of the test. Direct comparison between stroke and stroke-matched normal groups was also possible

TABLE 5. IMPAIRMENT DIFFERENCES IN PERFORMANCE BETWEEN STROKE AND NORMAL GROUPS

	Session 1· 11 days poststroke			*Session 11: 12 months poststroke*		
	Symptomatic arm[a]	*Asymptomatic arm*[b]		*Symptomatic arm*[a]	*Asymptomatic arm*[b]	
Test	*Measured*	*Measured*	*Adjusted*[c]	*Measured*	*Measured*	*Adjusted*[c]
Visual resolution (bit)		−0.33§	−0.5 §			
Arrow perception (incorr.)		0.50	0.25			
Static perception (incorr.)		2.92*	1.50			
Dynamic perception (incorr.)		3.54**	2.62*			
Joint movement sense (mm)	2.94***	0	0	1.8*	0	0
Grip strength (kg)	26.2***	5.5	6.8§	16.2**	1.7	3.1
	(66%)	(13 2%)	(16.5%)	(41%)	(4.2%)	(7.6%)
Arm strength (N)	63.6***	20.9§	25.5§	51.0**	15.9	20.5§
	(63%)	(20%)	(25%)	(45%)	(13.3%)	(17.2%)
Reaction time (ms)	234***	87.9**	92.7**	135.3*	36.4§	41.2*
	(100%)	(36%)	(38%)	(56%)	(14.6%)	(16.5%)
Speed (deg/s)	628***	285***	195**	421***	242**	152§
	(63%)	(28%)	(19.5%)	(42%)	(23%)	(14.5%)
Steadiness (mdeg/s)	1265***	9	−12	809**	29**	−3[d]
Steady movement (deg/s)	9.18***	2.34***	2.41***	5.93***	0.79**	0.87**
	(334%)	(96%)	(99%)	(242%)	(31%)	(34%)
Random tracking (bit)	51.9***	17.2***	13.9**	28.0***	7.05**	3.77§
	(350%)	(96%)	(78%)	(323%)	(77%)	(41%)
Step tracking (bit)	34 2***	15.4***	14.1**	26.6**	7.46**	6.15**
	(98%)	(41%)	(38%)	(89%)	(25%)	(21%)
Combination tracking (bit)	65.0***	26.6***	23.1***	55.4**	9.36**	5.88*
	(134%)	(63%)	(55%)	(163%)	(30%)	(18.9%)
Clinical deficit 'CD'	45.1***	0.75**		33.2***	0.25	
Functional deficit 'FD'	57.7***	1.50**		37.8***	0.50	

All the above figures are differences between, not absolute values for, the stroke and normal groups. Values are positive if stroke group performance is inferior to normal group, irrespective of whether function is measured as performance or error. Percentage differences (in parentheses) are with respect to normal means and have been omitted for nonsensical 'error' scores due to zero (CD, FD) or near zero (joint movement sense, steadiness) 'ceiling' scores for normals. Bilateral nonmotor measures are listed under the asymptomatic arm, to emphasize that both arms were equally affected. Visuospatial functions were not reassessed at the final session. Significance of absolute differences by Mann-Whitney test

[a] 'Symptomatic arm difference' = symptomatic arm (stroke)—left arm (normal). [b] 'Asymptomatic arm difference' = asymptomatic arm (stroke)—right arm (normal). [c] Stroke impairment scores are adjusted for nonmatching by adding or subtracting the inferiority bias depending on whether performance or error score respectively (*see* Table 4). The 'adjusted' visuospatial scores are from a direct comparison of stroke and stroke-matched normal groups. [d] Loss of significance (** → n.s.) on adjustment of final session steadiness scores is considered to be due to inappropriateness of applying a constant absolute adjustment to data with a marked ceiling effect followed by nonparametric analysis, rather than reflecting lack of impairment (as 4 stroke subjects had perfect '0' scores [illegible]

on session 1, and resulted in loss of and reduction in significance for static perception and dynamic perception, respectively. This confirms that any visuospatial impairment in the stroke group was mild.

At the first session, the symptomatic arm in the stroke group was inferior to controls on all quantitative tests and clinical deficit scores. With the exception of joint movement sense, the same was true for the so-called 'nonaffected' arm. Ipsilateral deficits of grip and arm strength were, however, of marginal significance ($P < 0.1$). For all quantitative tests, ipsilateral arm deficits were much less than contralateral ones.

Steadiness was an apparent anomaly as difference and significance between the groups increased over 12 months. While worsening in the nonparetic arm cannot be discounted, it seems more likely that this result is in error and that steadiness was impaired at 11 days.

At 12 months, the symptomatic arm was also inferior to controls on all lateralized quantitative tests scores. Similarly, arm strength, reaction time, speed, steadiness, steady movement and all 3 tracking tasks, remained impaired in the asymptomatic arm, although arm strength, speed and random tracking were only marginally affected. Grip strength, however, was normal ipsilaterally. Clinical scores (CD and FD) for the symptomatic arm were still inferior overall in the stroke group at 1 yr. However, 3 patients had normal function (FD = 0), 2 had mild deficits (FD < 25) and 3 remained densely hemiparetic (FD > 81). There was no deficit in clinical scores in the asymptomatic arm.

Comparison of quantitative and clinical impairment scores

Probability values obtained for CD and FD were identical on first and final sessions. As FD is a weighted subset of CD, its sensitivity to impairment cannot be improved near the zero impairment level. If CD is zero, so must FD. Hence neither CD nor FD is superior to the other in detection of impairment (differences in their magnitudes are not relevant as they are only incomparable ranking measures).

At the first session, 4 stroke subjects had nonzero CD scores on the asymptomatic arm. These were derived solely from mild deficits in higher mental function: 2 had nonspecific mental slowing, 1 had right/left discriminatory impairment, 1 had subtle left visual inattention and 2 had constructional dyspraxia. All other clinical tests of asymptomatic arm function were normal. Thus impaired asymptomatic arm performance on all quantitative motor tests indicates that they are more sensitive than CD to these types of deficits, or that impaired asymptomatic arm performance results from abnormalities in higher mental function. That the former is at least partly true is suggested by inability of clinical assessment of strength, speed and coordination to detect the absolute impairment demonstrated on related quantitative motor tests (strength, reaction time, speed and steady movement) in the asymptomatic arm of individual patients or the overall group.

Twelve months later, only 1 patient had a nonzero asymptomatic arm CD (Case

8 had a degree of constructional dyspraxia) and, in contrast to QSMB functions, the overall CD was nonsignificant. Thus although all motor tests in QSMB, except grip strength, remained significantly impaired (arm strength, speed and random tracking only marginally so), clinical examination did not reveal any significant deficit of arm function, either directly (via lateralized arm scores) or indirectly (via higher mental function scores) in the overall group.

Effect of nonmatching biases

Elimination of nonmatching on session 1 resulted in only minor changes (Table 5). Most notable were decreased visuospatial deficit and marginal impairment of grip strength in the asymptomatic arm (16.5%, $P < 0.1$).

Except for steadiness (*see* Note 'd' in Table 5), all asymptomatic arm functions impaired at 12 months (i.e., reaction time, speed, steady movement and random, step, combination tracking) retained significance to at least the $P < 0.1$ level after

TABLE 6 NEUROLOGICAL RECOVERY DIFFERENCES IN AVERAGE INCREMENTS BETWEEN STROKE AND NORMAL GROUPS

Test	*Asymptomatic arm*
Grip strength (kg)	0.24 (45%)
Arm strength (N)	−0.04 (−0.7%)
Reaction time (ms)	8.0* (195%)
Speed (deg/s)	6.6 (25%)
Steadiness (mdeg/s)	2 (100%)
Steady movement (deg/s)	0.30** (223%)
Random (%)	1.30** (21%)
Step (%)	1.20* (48%)
Combination (%)	2.05*** (68%)
Clinical deficit (CD)	0.10**
Functional deficit (FD)	0.20**

'Average increment' is the average performance increment per session over the 12-month trial. It is calculated from record scores and is an absolute value, except for tracking in which percentage increments are more appropriate (Jones, 1987). Record, rather than raw, scores have been chosen as they give better separation of neurological recovery from practice (Jones, 1987). Differences for asymptomatic arm are relative to right arm of normal group. Percentage differences (in parentheses) are with respect to normal mean; these have been omitted where nonsensical due to zero scores for normals. In contrast to impairment data, increments and probabilities remain unaffected by adjustments for nonmatching. Significance of absolute differences by Mann-Whitney test * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$, all one-tailed.

adjustment. Differences increased slightly on grip strength, arm strength and reaction time, but grip strength remained nonsignificant and arm strength became only marginal ($P = 0.09$). Conversely, the significance of impairment was reduced slightly for combination tracking and markedly for speed and random tracking.

In summary, adjustment for age, sex, driving experience and starting-hand differences between stroke and multiple session normal groups did not reveal or eliminate asymptomatic arm impairment at 12 months, although there were increases and decreases in magnitude and level of significance of several functions.

Neurological recovery

Significant improvements in performance above that seen with normal learning, implying neurological recovery, occurred over 12 months in the asymptomatic arm of the stroke group on reaction time, steady movement, random tracking, step tracking, combination tracking, CD and FD (Table 6). Although grip strength, arm strength, speed and steadiness were impaired initially, they did not show significant recovery. It is not clear whether these tests are less sensitive or whether such functions are resistant to recovery. CD and FD have the same sensitivity to recovery, as the difference between these scores (Table 6) is entirely due to a nonvarying scaling factor of '2' (Table 3).

DISCUSSION

Impairment of ipsilateral and bilateral sensory-motor function following unilateral cerebral lesions

Clinical examination initially found mild higher mental function involvement (4 of the 8 stroke subjects), although no direct asymptomatic arm impairment, but by 12 months no significant higher cerebral or ipsilateral deficit remained overall. Conversely, all QSMB tests of asymptomatic arm function, except for grip strength, showed significant impairment throughout the 12 month period.

Major reasons for not detecting ipsilateral deficits in clinical practice are their relative subtlety, failure to use sensitive tests (Brodal, 1973), use of the asymptomatic arm as the reference for impairment in the symptomatic arm and the emphasis placed on the symptomatic arm in rehabilitation.

Subject numbers are too small to allow meaningful comparison between the two hemispheres and the site and severity of lesions in either hemisphere were not comparable (*see* Table 1).

This study and its findings relate to current knowledge on ipsilateral and bilateral aspects of S-M control as follows.

1. Except for grip strength and steadiness, all QSMB functions were physically and conceptually different from those in other studies. Emphasis was on arm (proximal) rather than hand (distal) function. The new tests are arm strength, arm

reaction time, ballistic arm speed, steady movement, smooth preview tracking (full planning possible), step tracking (spatially and temporally unpredictable stimuli), combination of preview and step tracking, and joint movement sense.

2. Grip strength was marginally impaired ipsilaterally, if only for a week or two poststroke. This concurs with Glees and Cole (1952) who found ipsilateral grip strength deficits, following experimental lesions in motor cortex of monkeys, recovered to preoperative levels within 2 wks. Several studies in man (Kimura, 1977; Haaland and Delaney, 1981) have also found no grip strength deficit after several months, but others (Dodrill, 1978; Finlayson and Reitan, 1980; Hom and Reitan, 1982) have suggested possible long-term ipsilateral impairment.
3. Ipsilateral arm strength was marginally impaired throughout the 12 month poststroke period and this has not been previously noted.
4. Joint movement sense was not impaired ipsilaterally. This conflicts with other studies which found somatic sensation significantly impaired ipsilaterally (Semmes *et al.*, 1960; Vaughan and Costa, 1962). However, neither of these studies measured joint movement sense but concentrated on pressure threshold and two-point discrimination.
5. Ipsilateral reaction time, speed, steadiness, steady movement, random tracking, step tracking and combination tracking were impaired throughout the 12 month poststroke follow-up period.
6. On all QSMB and clinical tests, contralateral function was more impaired than ipsilateral function, as expected from the contralateral predominance of the somatosensory and motor pathway projections.
7. Significant but incomplete recovery was demonstrated ipsilaterally for reaction time, steady movement and all three forms of tracking over the 12 month poststroke period. Lack of recovery in strength, speed and steadiness may indicate less reversibility after stroke. No other studies have measured degree of recovery of ipsilaterally impaired S-M function.
8. The only deficit detectable on clinical examination, which could affect ipsilateral function, was a mild nonlateralized (i.e., not arm specific) disturbance of higher mental function and at 12 months this had resolved (except for 1 case with a degree of constructional apraxia). There has been no previous clinical and quantitative comparison on ipsilateral function.
9. These patients had unilateral cerebral hemisphere strokes resulting in contralateral arm weakness but with higher cerebral functions largely spared. Other studies have placed little restriction on subjects other than including predominantly unilateral cerebral disease (stroke, tumour, trauma).

This study differs from previous reports of nonpraxic motor function in the ipsilateral arm following cerebral hemisphere lesions. The majority of these studies have not verified lesions by CT and in none have all patients had CT scans. In only two studies (Semmes *et al.*, 1960; Haaland *et al.*, 1977) has there been a single pathology and each (trauma and tumour, respectively) could have had possible effect on both hemispheres. In fact, in all studies but one (Semmes *et al.*, 1960) tumours have been included. Many tumours produce bilateral effects through a variety of mechanisms. These include compromise of the opposite hemisphere through midline shift, ventricular obstruction and dilatation and malignant infiltration across the corpus callosum. Although it is not possible totally to exclude minor lesions in the opposite hemisphere by imaging techniques, the present study is the first to examine patients with a single pathology and to screen for subclinical contralateral hemisphere lesions or compression by CT scan in every patient.

This study is also the first to screen subjects for the presence of higher mental function deficits that may have an influence on the performance of sensory-motor tasks. Ideally, the patients should have had no deficit of higher mental function. If, however, testing is comprehensive enough, it is likely some such abnormality can be found in virtually every patient with cerebral infarction. Thus screening in the present study was to exclude subjects with other than mild deficit of higher mental function. The small number of patients ($n = 8$) was selected after evaluating all stroke admissions to two large general hospitals over an 8 month period. We believe demonstrated deficits in ipsilateral upper-limb S-M performance were not due to the mild abnormalities in higher mental function as these seem unlikely to affect such simple motor activities as strength, movement speed, steadiness and steady movement, nor produce a deficit in reaction time and tracking of the extent seen. In addition, these abnormalities in S-M performance persisted for 12 months after the stroke when signs of impaired higher mental function had resolved in all but 1 patient.

Mechanisms of ipsilateral and bilateral control of sensory-motor function

Ipsilateral deficits after unilateral cerebral lesions could be due to direct ipsilateral input to lower motor neurons or involve the contralateral hemisphere with its crossed corticospinal output. Interhemispheric connections are well established but what evidence is there for direct ipsilateral pathways?

Although most corticospinal fibres decussate in the medulla to form the contralateral lateral corticospinal tract, 25% remain uncrossed (Nyberg-Hansen and Rinvik, 1963; Yakovlev and Rakic, 1966; Brodal, 1981). Of these, 15% continue as the ventral corticospinal tract (Nyberg-Hansen and Rinvik, 1963) which mainly decussates in the spinal cord to innervate the contralateral side (Noback, 1967). The remaining 10% of uncrossed fibres stay in the ipsilateral lateral corticospinal tract (Glees and Cole, 1952; Nyberg-Hansen and Rinvik, 1963; Brodal, 1981) and might contribute ipsilateral input if they supply the arm. The same applies to corticospinal fibres which decussate at the medulla but recross in the spinal cord, as has been demonstrated for the lower limbs (Nathan and Smith, 1973). The possibility of multiple decussations within the cord has also been shown by the effects of two unilateral cordotomies in cats (Jane *et al.*, 1964) and man (Nathan and Smith, 1973). Nathan and Smith concluded that the lateral corticospinal tract carried the majority of ipsilateral fibres, as recovery of the limb on the side of the first cordotomy occurred even when alternative corticofugal pathways, such as rubrospinal and reticulospinal tracts, were severed bilaterally.

Support for ipsilateral control also comes from studies of suprapyramidal lesions. After destroying 83% of corticospinal fibres in one cerebral peduncle, Bucy *et al.* (1964) observed effectively full recovery from contralateral hemiplegia. It is possible, however, that such recovery was due to intact pathways remaining on the lesioned side. After the second operation in staggered unilateral sections of corticospinal tracts in both cerebral peduncles in monkeys, the deficit due to the initial surgery was increased, demonstrating bilateral influence of each corticospinal tract (Bucy *et al.*, 1966).

Further evidence for ipsilateral cortico-limb pathways has been gained from split-brain studies in which contralateral hemisphere effect can be discounted. Following complete section of neocortical commissures, both hemispheres are able to produce ipsilateral and contralateral movement (Gazzaniga *et al.*, 1967; Brinkman and Kuypers, 1973). Ipsilateral control appears strongest for axial and proximal limb musculature and weakest for individual finger movements, especially of the right hand (Gazzaniga *et al.*, 1967). These observations are in keeping with Brodal's (1973) contention that the corticospinal supply to the hand is almost entirely contralateral, as appears to be the case in the monkey (Kuypers and Brinkman, 1970).

An important distinction between studies of ipsilateral function using neocortical commissurotomies and those involving unilateral lesions is that the contralateral system is intact only in the former. This, together with the minor disturbance of ipsilateral movement in split-brain subjects, suggests a third possible mechanism for ipsilateral control, namely modulation of the contralateral system via subcommissural pathways from the other (ipsilateral to limb) hemisphere.

Two apparent paradoxes remain largely unexplained. If ipsilateral pathways produce such substantial recovery in contralateral limbs following unilateral spinal cord or cerebral peduncle lesions, why are ipsilateral deficits so subtle after unilateral cerebral lesions? Studies of subhemispheric unilateral lesions, including the pyramidal tract in the medulla in monkey (Tower, 1940) and man (Ropper *et al.*, 1979), have not observed ipsilateral deficits. Secondly, why do ipsilateral pathways not facilitate similar recovery following internal capsule lesions in which contralateral limb deficits may be severe and irreversible? The first paradox may be explained by suppression of ipsilateral pathways when the contralateral system is intact, as has been suggested in split-brain studies (Gazzaniga *et al.*, 1967). In the second paradox, severity of deficit following capsular lesions probably reflects disruption to other corticofugal tracts, which are more intermingled with corticospinal fibres than at the level of the pyramids (Brodal, 1981). This cannot, however, explain the failure of ipsilateral pathways largely to prevent hemiparesis from such lesions.

Our results suggest three conclusions regarding the bilateral control of S-M functions.

First, all cerebral hemisphere areas involved in S-M functions can exert some degree of bilateral motor control. Of the wide range of S-M functions tested in this study, all were impaired bilaterally by unilateral lesions, although only marginally so for grip and arm strength. Substantial support for this conclusion has also been provided by several other studies (Vaughan and Costa, 1962; Carmon, 1971; Wyke, 1971; Heap and Wyke, 1972; Dodrill, 1978; Haaland and Delaney, 1981).

Secondly, ipsilateral influence is never greater than contralateral influence, and in many cases is considerably less. There were no exceptions to this in our study, although potential exceptions exist. For example, it has been proposed that visuokinetic engrams from left parietal lobe travel intracerebrally to left premotor cortex (for right arm control) and then intercerebrally to right premotor cortex (for left arm control) (Heilman *et al.*, 1982). Thus frontocallosal lesions may produce ideomotor praxic deficits which are greater, or solely, in the ipsilateral left arm (Geschwind and Kaplan, 1962; Watson *et al.*, 1986; Watson and Heilman, 1983; Graff-Radford *et al.*, 1987). In none of the above cases, however, has the lesion been confirmed as being strictly unilateral, as midline structures were affected.

Thirdly, the proportion of ipsilateral to contralateral cerebral control is closely related to the degree of continuous sensory feedback (visual, proprioceptive, tactile) required by the particular task (Haaland and Delaney, 1981). Thus as the complexity of a S-M task increases so does dependence on bilateral cerebral hemisphere function. Of functions tested, grip and arm strength were least impaired ipsilaterally in keeping with strength tests requiring minimal S-M skill and depending minimally on ipsilateral cerebral involvement. Speed is the only other QSMB test not requiring continuous S-M feedback. This task is of relatively low complexity and ipsilateral impairment was marginal. All QSMB tests requiring continuous sensory feedback, that is, reaction time, steadiness, steady movement and the 3 tracking tasks, were significantly impaired ipsilaterally. Furthermore, the degree of impairment tended to reflect complexity of sensory and motor requirements. Steadiness and steady movement can be performed with eyes closed. Thus visual input is not essential but the tasks need continuous proprioceptive feedback. Reaction time utilizes most elements of the S-M system, ensuring it of a bilateral influence. Simplicity and brevity, however, minimize the integration involved, resulting in mild ipsilateral impairment (16% at 12 months). In keeping with the complexity of tracking, ipsilateral impairment on the 3 tracking tasks was greater than for other QSMB tasks ranging from 19% to 41% at 12 months.

Although a gross simplification, we suggest that the present pattern of severe contralateral and milder ipsilateral deficits after unilateral cerebral hemisphere stroke can be explained by a 3-tier cerebral model of S-M integration (fig. 2). 'Lower' level cerebral functions have effects which are strongly lateralized to the

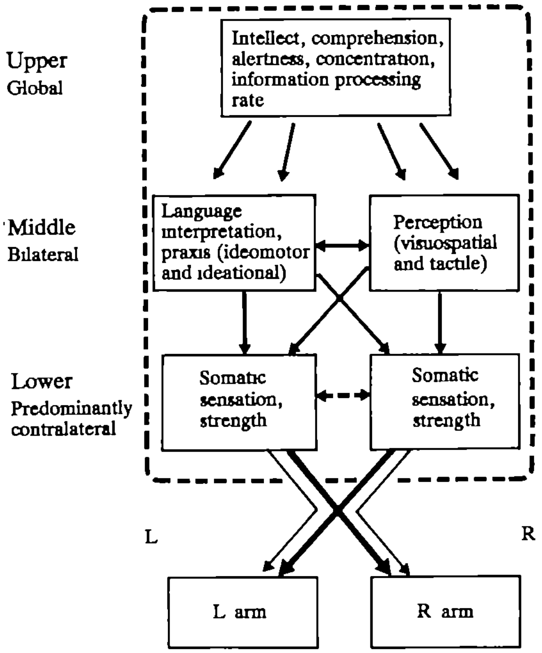

Upper
Global
Middle
Bilateral
Lower
Predominantly contralateral
Intellect, comprehension, alertness, concentration, information processing rate
Language interpretation, praxis (ideomotor and ideational)
Perception (visuospatial and tactile)
Somatic sensation, strength
Somatic sensation, strength
L
R
L arm
R arm

FIG. 2 Proposed 3-tier cerebral model of sensory-motor integration (*see* text for details).

contralateral limbs and have well-defined cortical representation, for example, somatic sensation (postcentral gyrus) and strength (precentral gyrus). In contrast, 'middle' level cerebral functions have effects which are bilateral and influence the lower level in both hemispheres nearly equally. The site of these functions is not well defined but lies principally within the parietal lobes and is partially lateralized. The left hemisphere appears dominant for language interpretation (Lezak, 1976; Walsh, 1978; Brodal, 1981), ideational praxis (Heilman, 1973) and ideomotor praxis (Heilman *et al.*, 1982; Kertesz and Ferro, 1984; Watson *et al.*, 1986; Graff-Radford *et al.*, 1987). The right hemisphere is dominant for visuospatial perception (Lezak, 1976; Walsh, 1978) and tactile perception (Boll, 1974). Finally, 'upper' level cerebral functions have contralateral and ipsilateral effects which are essentially equal. These functions are diffusely sited and include intellect, comprehension, alertness, concentration, and information processing rate. They may be affected by lesions at various cerebral sites, particularly if diffuse, bilateral, or involving the ascending reticular activating system. Their influence is global and impairment can degrade performance of functions at any lower level.

Most ipsilateral arm deficits can be explained by the degree to which various components of the S-M system (as depicted in fig. 2) are required to perform particular tasks. Overriding factors are the predominance of contralateral projections for somatosensory and motor functions at the lower level, and multiplicity of intra- and interhemispheric connections at higher levels.

Overall, evidence from this and other studies indicates unequivocal impairment of ipsilateral arm function on a wide range of simple and complex sensory-motor tasks following unilateral cerebral lesions. The same principles may also apply to lower limb function. Although some recovery occurs, certain deficits may persist, even after several years. These are unlikely to be detected by standard clinical examination. Awareness of impaired ipsilateral function may be important in rehabilitation.

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THE NATURAL HISTORY OF MULTIPLE SCLEROSIS: A GEOGRAPHICALLY BASED STUDY

I. CLINICAL COURSE AND DISABILITY

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SUMMARY

The outcome of multiple sclerosis (MS), assessed according to the Kurtzke Disability Status Scale (DSS), was reviewed in 1,099 consecutive patients followed in London, Canada, between 1972 and 1984. A geographically based subgroup of 196 patients representing 90% of Middlesex County MS patients as well as a group of 197 patients seen from onset of disease were separately analysed. The clinical course was progressive from onset in 33% of the total population and in 28% of the Middlesex County subgroup. Of those with duration of 6–10 yrs, 30–40% with initially remitting disease developed progressive MS. The cross-sectional distribution of disability was bimodal with peaks at DSS 1 (no disability) and DSS 6 (assistance required for walking). Actuarial analysis showed that the median time to reach DSS 6 from onset of MS was 14.97±0.31 yrs in the total population and 9.42±0.44 yrs in the 'seen from onset' subgroup. Survival was minimally altered; 87% of patients followed up to 40 yrs were still alive, although ascertainment of cases with this duration of MS was incomplete. Data describing the rate at which disability develops after the onset of a progressive phase of MS are also presented. The implications of these data in planning and interpretation of clinical therapeutic trials are discussed.

INTRODUCTION

In general, studies that have attempted to define the natural history of multiple sclerosis (MS) have drawbacks arising from mechanisms of patient ascertainment and follow-up. Hospital-based series are biased toward severe cases (Poser *et al.*, 1982*a*). Clinic-based studies are often not geographically based (McAlpine and Compston, 1952; Patzold and Pocklington, 1982; Verjans *et al.*, 1983; Thompson *et al.*, 1986). They are subject to the referral biases of physicians in the community who may not refer the minimally disabled or the institutionalized patient to an MS clinic where natural history data are collected. With rare exceptions (Kurtzke

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et al., 1977), completeness of follow-up and reasons for patient attrition are infrequently documented. The duration of longitudinal observation is frequently too short to make definitive statements as to outcome (Patzold and Pocklington, 1982), or the analysis of disability is cross-sectional (Leibowitz *et al.*, 1964; Panelius, 1969; Verjans *et al.*, 1983). Prospective studies of an 'inception cohort', a group of patients assembled at an early and uniform point in the course of their illness (Sackett *et al.*, 1985), are unrealistic; many patients do not present for years after their first symptoms, and the duration of follow-up required is too long, given the generally slow evolution of MS. Furthermore, widespread participation in clinical trials aimed at altering the natural history of MS have all but eliminated the opportunity for conducting prospective studies of outcome in an unselected population. We have proposed strategies to improve the validity of studies of natural history in MS (Weinshenker and Ebers, 1987). These include (1) geographically based surveys so as to ascertain all cases of MS in the community, (2) separate analysis of patients seen from onset of MS for whom ambiguity in determining the onset of MS and referral bias based on outcome are less likely to play a role, (3) longitudinal evaluation, (4) avoidance of systematic loss of patients to follow-up due to increasing disability, (5) use of a sensitive yet meaningful measurement of outcome. A recent review discusses methodological problems and results from several previous studies of natural history (Weinshenker and Ebers, 1987).

We report our results based on the longitudinal follow-up of 1,099 consecutive MS patients evaluated at the MS Clinic of University Hospital, London, Canada, between 1972 and 1984. Of these patients, 197 were followed by a neurologist from the onset of disease and clear documentation of the details of their early clinical course was available; ambiguity in determining the onset of MS is likely to be minimal in this group. Furthermore, 196 patients were resident in Middlesex County. A separate study of prevalence of MS in this area has confirmed that 90% of patients in Middlesex County were registered with our clinic (Hader *et al.*, 1988). While retrospective, data for this study were collected serially with the intent of undertaking this review. Our data on the subgroup followed from onset of disease were essentially collected prospectively.

METHODS

The London MS Clinic

The MS Clinic at the University Hospital in London, Canada, was established in 1972 to provide ongoing care for MS patients in its referral area of Southern Ontario. The pattern of practice in London is such that all neurologists are members of the University system, and refer all patients with MS to our clinic for long-term follow-up. Although it is a tertiary referral centre, the London MS Clinic retains a geographically based character, which is most completely documented in Middlesex County. The prevalence of MS in Middlesex County as of January 1, 1984 was 95/100,000 and the incidence was 3 5/100,000 between 1975–1979. Mortality was 1.4/100,000. Half of the deaths were directly attributed to MS (Hader *et al.*, 1988). Patients are evaluated annually by 1 of 4 neurologists whose primary interest is MS. Patients continue to be followed once institutionalized in nursing homes and every attempt is made to determine the reason for which a patient might become 'lost to follow-up'. No specific treatment other than corticosteroids for acute exacerbations was given during the course of this study. Steroids are not generally felt to alter the natural history of MS (Matthews *et al.*, 1985).

Records on our total population of 1,099 patients followed from 1-12 yrs were reviewed between 1979 and 1984. Two subgroups were identified. The Middlesex County subgroup represented a population-based group for which ascertainment was near complete: 90% of patients in Middlesex County were registered in our clinic (Hader *et al.*, 1988). Those patients not registered were largely chronically institutionalized patients, most of whom were severely disabled before our clinic was established. The 'seen from onset' (SO) subgroup consisted of 197 patients seen by a neurologist from their first symptom Of these, 114 were seen in our clinic within 12 months of diagnosis. Only 49 were first seen 2 or more yrs after diagnosis. Disability in these patients was generally low when first seen in our clinic; only 6/49 had disability exceeding level 3 on the Kurtzke disability status scale (DSS) (Kurtzke, 1961) and only 1 had disability exceeding DSS 6. As such, we feel that the SO subgroup is relatively unbiased by referral for disability, which is a common cause for referral in the total population.

Data collection

Research charts separate from patients' hospital records are kept and standard data forms are completed at each patient visit. Patients are followed annually or semiannually regardless of their clinical course. Quantitation of disability was done retrospectively on patients for visits which took place in the early years after establishment of the clinic. The following details of the clinical and demographic features of our clinic population were recorded: age at onset; sex; diagnostic certainty (possible, probable) according to accepted criteria (Poser *et al.*, 1983); initial symptoms; functional system (i.e., spinal cord, brainstem, etc.) involved at the time of the first and second attacks. HLA typing results and family history of MS (affected first, second or third degree relative) were also recorded, as were abnormalities on evoked responses and CSF analysis. The following details regarding the temporal course were recorded: type (relapsing/remitting, relapsing/progressive, chronically progressive, or combinations thereof); number of attacks in the first year and second year of disease; the interval between the first and second attack; the interval from onset at which the course became progressive. Outcome was measured according to scales proposed by Kurtzke (1961). Outcome measurements were recorded as follows: score on the DSS at final assessment; Kurtzke Functional Scores at final assessment; and time to reach each successive level of disability according to the DSS.

The final evaluation of patients for this study occurred during the period of record review (1979-1984) in 83.4% of the total population and 96.4% of the SO subgroup attesting to the regularity and completeness of follow-up.

Data were recorded on standardized forms and entered on a mainframe computer. The statistical program SAS (SAS Institute Inc., Cary, North Carolina) was used for data analysis including actuarial analysis of progression of disability.

RESULTS

Demographic characteristics

The demographic characteristics of the total population and the two subgroups considered are shown in Table 1. The average duration of disease was 11.9 ± 0.3 (SEM) yrs in the total population. The mean duration of follow-up in the SO subgroup was 4.2 ± 0.2 yrs. The subgroups otherwise closely resembled clinic population in age, sex ratio and diagnostic certainty.

TABLE 1 CHARACTERISTICS OF PATIENT SUBGROUPS

	TP	*MC*	*SO*
No. of patients	1099	196	197
No. of males	377	63	62
females	722	133	135
Sex ratio (M/F)	0.52	0.47	0.46
Diagnostic certainty			
Probable	916 (83.3%)	176 (89.8%)	162 (82.2%)
Possible	183 (16.4%)	20 (10.2%)	35 (17.7%)
Disease duration			
Mean (yrs ± SE)	11.9 ± 0.3	13.0 ± 0.6	4.2 ± 0.2
Median (yrs)	10	12	3
Age at onset			
Mean (yrs ± SE)	30.5 ± 0.3	28.0 ± 0.6	29.9 ± 0.7
Median (yrs)	29	26	28

TP = total population, MC = Middlesex County subgroup; SO = seen at onset subgroup.

Initial symptoms and signs

Initial symptoms and signs were grouped as follows: optic neuritis; sensory symptoms; motor deficit of acute onset; motor deficit of insidious onset; diplopia and/or vertigo (the most common symptoms reflecting brainstem involvement); limb ataxia and/or difficulty with balance (generally reflecting involvement of the cerebellum and/or cerebellar connections). The percentage of patients in our clinic population with each of the presenting clinical features stratified according to age at onset is shown in Table 2. The commonest presenting symptom was sensory impairment followed by optic neuritis and insidious motor deficit. Optic neuritis and sensory impairment were more common in younger patients, and motor deficit was more common in older patients. The initial presentation was very similar in the Middlesex County and SO subgroups (data not shown).

TABLE 2 INITIAL PRESENTATION IN TOTAL CLINIC POPULATION

		Percentage with initial presentation					
Age at onset (yrs)	*n*	*Optic neuritis*	*Sensory*	*Motor (acute)*	*Motor (insidious)*	*Diplopia and/or vertigo*	*Limb ataxia and/or impairment of balance*
<20	131	22.9	46.5	6.1	3.8	17.6	13.7
20–29	435	22.8	52.2	7.3	6.2	12.4	11.3
30–39	310	13.2	44.2	6.8	14.5	11.0	14.8
40–49	173	9.2	33.5	2.9	30.6	16.8	12.7
>49	47	6.3	31.9	4.2	46.8	12.8	10.6
Total	1096	17.2	45.4	6.2	13.9	12.9	13.2

Clinical course

The clinical course was classified into relapsing/remitting (RR), or progressive from onset, with (RP) or without (CP) superimposed acute episodes of worsening. The criterion for progressive disease was continuing deterioration without remission, regardless of the rate of deterioration. The distribution of patients at onset of their illness is shown in Table 3. Those with initially remitting disease are stratified according to duration so as to demonstrate the frequency of conversion from remitting to progressive disease (Table 4). Approximately 30% of the total population and the Middlesex County subgroup had either RP or CP disease from onset; only 15% of patients in the SO subgroup were so classified. This disparity possibly reflects a tendency for patients who are seen for the first time at a later point in their illness to discount or forget earlier remitting symptoms when progressive disease intervenes subsequently. It is our experience that a patient may recount a remote first attack only after several previous clinic visits. To a large extent, however, the disparity may reflect the definition of 'seen at onset' which tends to exclude those with insidious onset of disease as often occurs in patients with CP disease from onset.

The percentage of patients who convert from RR to progressive disease increases

TABLE 3 CLINICAL COURSE AT ONSET OF DISEASE

	TP		*MC*		*SO*	
	n	%	*n*	%	*n*	%
Relapsing/remitting	722	65.8	138	70.4	166	84.7
Relapsing/progressive	162	14.8	35	17.9	14	7.1
Chronically progressive	205	18.7	23	11.7	15	7.7
Data unavailable	10	0.9	0	0.0	2	1.0
Total	1099		196		197	

TP = total population; MC = Middlesex County subgroup; SO = seen at onset subgroup.

TABLE 4 FREQUENCY OF CONVERSION FROM REMITTING TO PROGRESSIVE MS

Duration of MS at final review (yrs)	*Percentage of patients who convert to progressive MS (n)*		
	TP	*MC*	*SO*
1–5	12.1 (231)	8.8 (34)	10.3 (126)
6–10	41.3 (179)	29.4 (34)	42.4 (33)
11–15	57.6 (118)	53.8 (26)	28.6 (7)
16–25	65.6 (131)	72.7 (33)	— (0)
26+	88.9 (63)	90.9 (11)	— (0)
Total	(722)	(138)	(166)

TP = total population; MC = Middlesex County subgroup, SO = seen at onset subgroup; n = number of patients (in brackets) with remitting disease at onset.

steadily with duration. After the first decade of disease, over half of patients whose disease was initially remitting entered a progressive phase of MS. Approximately 90% of 63 patients in the total population with initially RR disease and duration longer than 25 yrs had developed progressive disease. In the SO subgroup, only 10.3% of patients had converted from RR to progressive MS within 5 yrs, but of 40 patients followed from 6–15 yrs from onset, 40% had developed progressive MS.

TABLE 5 PROGRESSIVE MS FROM ONSET ACCORDING TO AGE

Age at onset (yrs)	*Percentage of patients progressive at onset (n)*		
	TP	*MC*	*SO*
<20	17.6 (131)	13.0 (23)	14.3 (21)
20–29	19.1 (435)	17.9 (84)	8.6 (105)
30–39	37.7 (310)	37.0 (54)	14.6 (48)
40–49	63.0 (173)	63.0 (27)	36.8 (19)
>49	74.5 (47)	37.5 (8)	100.0 (3)
Data unavailable	(3)	(0)	(1)
Total	(1099)	(196)	(197)

TP = total population; MC = Middlesex County subgroup; SO = seen at onset subgroup, n = number of patients (in brackets) in each category

The clinical course varied according to age at onset as shown in Table 5. There was an increase in the percentage of patients with progressive disease from onset with each decade. The majority of patients whose disease began in the fifth decade of life or later had progressive disease from onset.

Disability

Cross-sectional analysis. At the time of final review between 1979–1984, the distribution of disability in our clinic population is shown in Table 6. In the Middlesex County subgroup 53% had disability rated as less than DSS 6 and 47% had disability greater than or equal to DSS 6. This probably reflects the distribution of disability within a population of MS patients given the completeness of ascertainment within this geographic area.

Longitudinal analysis of disability from onset of MS. Outcome data are presented as an actuarial analysis, which was performed for key levels of disability: DSS 3 (moderate disability), DSS 6 (ambulatory but requiring walking aids), DSS 8 (restricted to bed but with effective use of arms), and DSS 10 (death due to MS) (fig. 1). Our data show a strong correlation between the DSS score and the pyramidal score of the Kurtzke Functional Scales (data not shown). The validity

TABLE 6. CROSS-SECTION OF DISABILITY AT FINAL REVIEW

	TP		*MC*		*SO*	
DSS	*n*	%	*n*	%	*n*	%
1	182	17	33	17	70	36
2	156	14	27	14	53	27
3	123	11	25	13	20	10
4	71	6	12	6	6	3
5	31	3	7	4	2	1
6	205	19	34	17	19	10
7	203	18	33	17	16	8
8	88	8	19	10	6	3
9	23	2	2	1	3	2
10	16	1	4	2	1	1
Data unavailable	1		0		1	
Total	1099		196		197	

DSS = Kurtzke Disability Scale Status; TP = total population; MC = Middlesex County subgroup; SO = seen at onset subgroup

of our data for the total population and Middlesex County subgroups beyond 12 yrs from onset of MS has limits imposed by the duration that our clinic has been in existence. Complete ascertainment was not possible for cohorts of patients with onset of MS before our clinic was established, resulting in exclusion of those who may have died or have been institutionalized before that point. However, the effect is possibly small in Middlesex County given the high degree of ascertainment of cases in the community and the low attributable mortality rate due to MS.

The median time for the total population to reach DSS 3 was 7.69 yrs, to reach DSS 6 14.97 yrs and to DSS 8 46.39 yrs. For the SO subgroup, the median time to reach DSS 3 was 6.28 yrs and to DSS 6 was 9.42 yrs (Table 7).

The differences between the data for Middlesex County subgroup and the total population were small (data not shown), suggesting that referral biases outside the geographic area of our clinic did not have a major effect on our results for the total population. While the mean follow-up in the SO subgroup was only 4.2 ± 0.2 yrs, these data were largely prospectively collected. The outcome in this

TABLE 7 TIME (YRS) FROM ONSET OF MS TO REACH SELECTED LEVELS OF DISABILITY (MEDIAN ± SE)

	TP	*MC*	*SO*
DSS 3	7.69 ± 0.42	9.04 ± 0.88	6.28 ± 0.34
DSS 6	14.97 ± 0.31	15.77 ± 0.38	9.42 ± 0.44
DSS 8	46.39 ± 0.14	33.02 ± 0.43	—
DSS 10	—	—	—

DSS = Kurtzke Disability Scale Status, TP = total population, MC = Middlesex County subgroup; SO = seen at onset subgroup

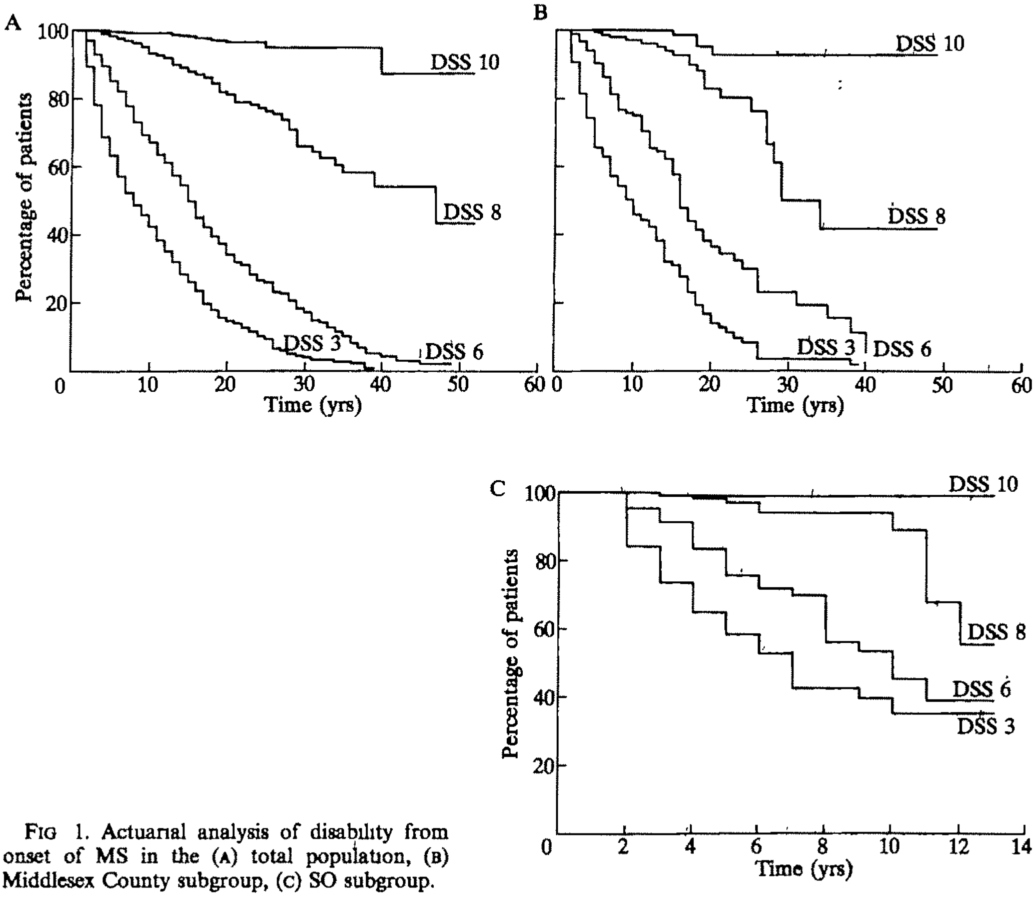

FIG 1. Actuarial analysis of disability from onset of MS in the (A) total population, (B) Middlesex County subgroup, (C) SO subgroup.

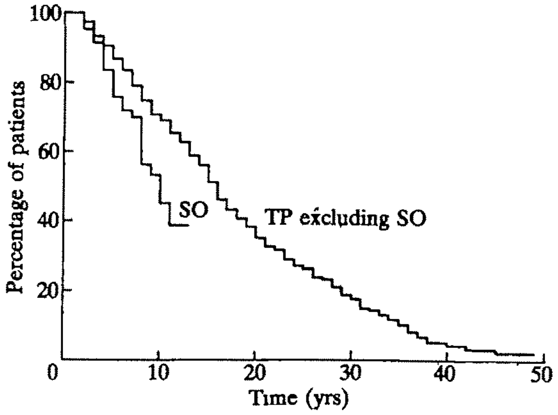

FIG. 2. Comparison of actuarial analysis for DSS 6 in the SO subgroup compared with the remainder of the clinic population. The outcome is worse in the SO subgroup (logrank $\chi^2 = 9.85$, $P < 0.01$). TP = total population. SO = seen from outset.

group was worse than that of the remainder of the clinic population as determined by the rate at which DSS 3, 6 and 8 were reached (fig. 2).

Longitudinal analysis of disability from onset of progressive MS. An actuarial analysis of progression of disability indexed to the onset of progressive disease is shown in fig. 3 for those patients who were classified as having progressive MS at or before each level of disability was reached. The onset of progressive deficit was often determined retrospectively, except for those patients followed from onset of disease, data for whom are shown in fig. 3c. The mean time from onset of MS to a progressive phase of the disease was 5.8±0.28 yrs for the total population, 7.14±0·74 yrs for the Middlesex County subgroup and 1.83±0.24 yrs for the SO subgroup. Patients whose disease became progressive within the relatively short period of follow-up in the SO subgroup are highly selected for those with the most aggressive disease. The median times to reach DSS 3, 6 and 8 from onset of progressive MS were 1.40 yrs, 4.50 yrs and 24.08 yrs, respectively,

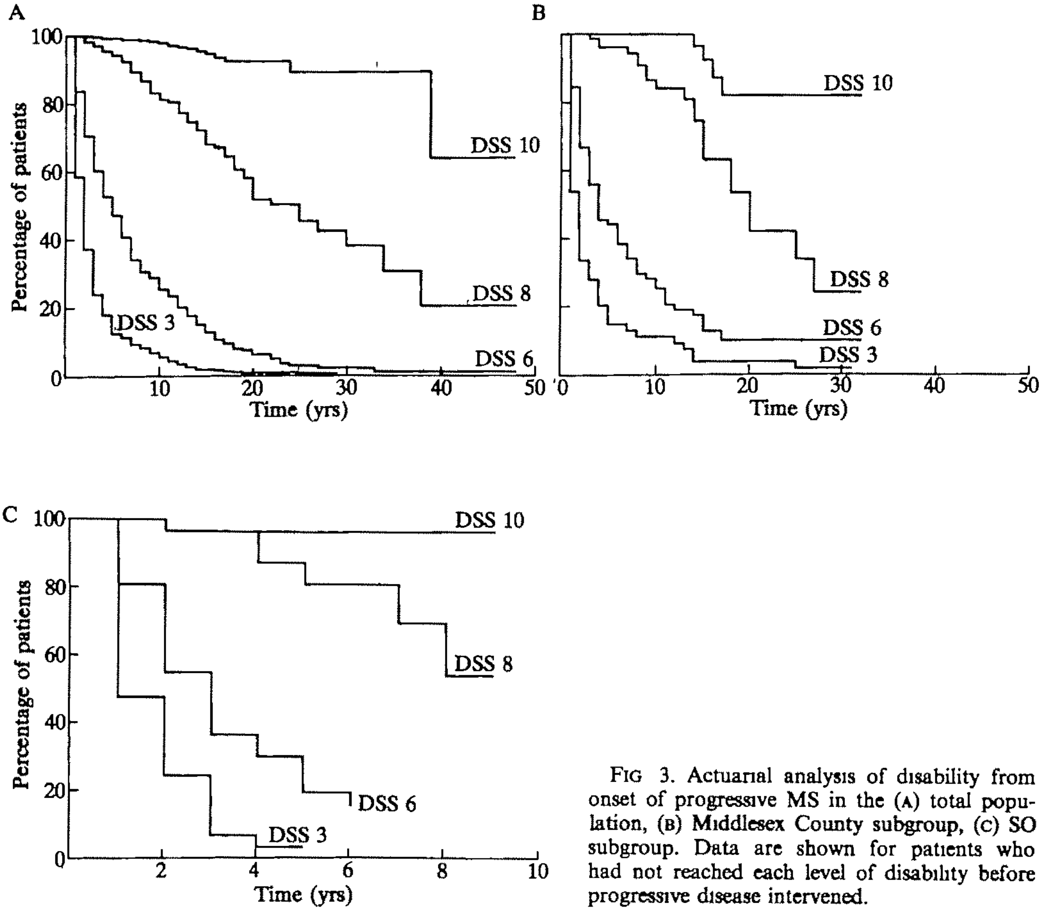

FIG 3. Actuarial analysis of disability from onset of progressive MS in the (A) total population, (B) Middlesex County subgroup, (C) SO subgroup. Data are shown for patients who had not reached each level of disability before progressive disease intervened.

TABLE 8 MEDIAN TIME (YRS) FROM ONSET OF PROGRESSIVE MS TO REACH SELECTED LEVELS OF DISABILITY (MEDIAN ± SE)

	TP	*MC*	*SO*
DSS 3	1.40±0.11	1.20±0.33	0.96±0.17
DSS 6	4.51±0.38	3.58±0.52	2.27±0.45
DSS 8	24.08±0.44	19.32±0.46	—
DSS 10	—	—	—

DSS = Kurtzke Disability Scale Status; TP = total population; MC = Middlesex County subgroup; SO = seen at onset subgroup.

for the total population. For the SO subgroup the median times to DSS 3 and 6 were 0.96 yrs and 2.27 yrs (Table 8).

We analysed the progression index (change in DSS per yr of disease) in the first 5 yrs after a progressive phase of MS had begun (fig. 4). The mean rate of change was 0·53±0·02 DSS points per yr; median rate of change was 0.40 DSS points per yr.

Mortality resulting directly from MS

Of our total clinic population of 1,099, 16 patients (1.5%) had died from MS-related causes (DSS 10). Cases of suicide were excluded. The mean duration to death from onset of MS in our total population was 15.1±2.6 yrs. Survival analysis, however, shows that the median survival time using DSS 10 as endpoint was greater than 40 yrs with 88% of patients not having reached DSS 10 at 40 yrs from onset of MS. Only 1/197 followed from onset died from causes related

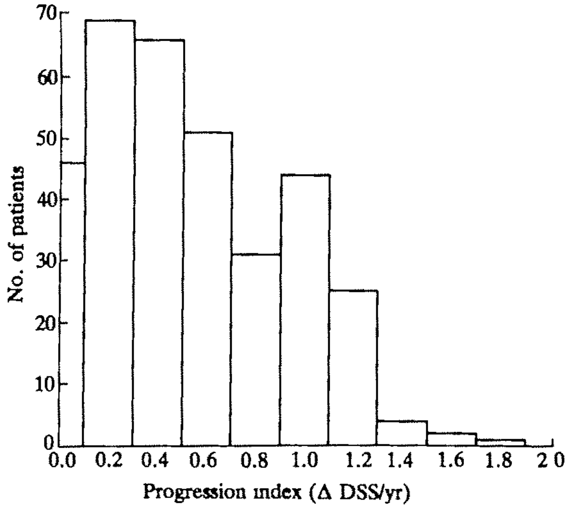

Fig 4 Frequency distribution of progression index (ΔDSS/yr) in the first 5 yrs after onset of a progressive phase of MS Data are shown for 339 patients for whom sufficient data were available for analysis.

to MS (0.5%) over the average period of follow-up of 4.2 ± 0.2 yrs; survival at 10 yrs exceeded 99% in this subgroup. Mortality data from our study are limited by the fact that the total population does not represent a cohort and by the limited duration of follow-up in the SO subgroup.

DISCUSSION

There are several aspects of this study which we feel are important. It is clinic based and provides data on longitudinal yearly follow-up of a very large population of MS patients. As a longitudinal study, it avoids the problem encountered in cross-sectional studies of recording fluctuations in disease activity which are of little significance to permanent disability. Furthermore, we have separately analysed our geographic referral base, Middlesex County, Ontario, where ascertainment of cases in the community is high (90%), due to a unique referral pattern from neurologists at our centre. Once patients were ascertained, follow-up was almost complete. By using disability data derived from physicians' examinations expressed in terms of increments on the DSS, the data available are more detailed than those found in other community-based studies which employed trained interviewers or mail questionnaires (Clark *et al.*, 1982; Detels *et al.*, 1982; Visscher *et al.*, 1984). Furthermore, the time to reach each successive level of disability was recorded. We thereby avoided the assumption that the DSS is an interval scale, unlike other studies which divide the DSS by duration to obtain a 'progression index' (Poser *et al.*, 1982*a*; Verjans *et al.*, 1983). Outcome data in this study have not been altered by any agents suspected to produce alterations in the natural history of MS. Because of increasing evidence that immunosuppressive treatment ameliorates the outcome of this condition, the opportunity to collect natural history data on the untreated course of MS is decreasing.

Just as the data of Poser *et al.* (1982*a*) disclose the biases of inpatient-based studies, our series raised the more subtle biases and difficulties inherent in clinic-based studies of a group heterogeneous in the duration of disease and length of follow-up. Such studies have been the basis of much of our understanding of the outcome of MS. The SO subgroup represented a group of patients for whom excellent documentation was available of the onset and early course of MS. Furthermore, patients in this subgroup were first seen at relatively low levels of disability, so that referral bias, based on adverse outcome, was minimized. Disability indexed to duration was less advanced in the total population than in the SO subgroup; this is particularly evident in the percentage who reach DSS 6. This could be explained in one of several ways. First, the fact that a patient was referred at presentation could be associated with a poor outcome; such patients often have multiple or severe symptoms at onset. Secondly, the data for the total population are spuriously favourable due to exclusion of some patients institutionalized or dead before our clinic was established and who did not come to our attention. Thirdly, the definition of the SO subgroup excludes patients with a long first remission who do not come to medical attention until years after their first symptoms; this biases our results towards a worse outcome. The percentage of patients who were determined historically to be progressive from onset was greater in the total population than in the SO subgroup; again, this is largely inherent in the definition of the SO subgroup, which tends to exclude patients with an insidious onset. Undoubtedly the accuracy of information is superior in this subgroup. This point emphasizes the difficulties inherent in analysis of retrospectively obtained historical information. Thus an analysis of cases seen from onset of their disease circumvents many biases associated with retrospective studies but may create others. Furthermore, a large population of patients must be followed to derive an adequate sample followed from onset of MS. In our study, only 20% of patients were first seen shortly after onset of MS.

We fail to show significant differences between the outcome of disease in a geographically-based population and the total population of MS patients followed in our clinic. This may be because most patients with MS who seek neurological evaluation in Southern Ontario are eventually seen in our clinic. The concept of a geographically-based study including data from all patients in the community may be an important one, however. The potential for generating unrepresentative results in a nongeographically-based study cannot be overlooked.

Based on life table analysis, 33% of our total population had reached DSS 6 at 10 yrs from onset of MS, as had 55% of the SO subgroup. Although not a completely ascertained cohort, 83% of patients followed 30 yrs from onset of MS had reached DSS 6 and 34% had reached DSS 8; 50% of patients with progressive disease reached DSS 6 in 5 yrs and DSS 8 in 22 yrs. This observation is consistent with the generally held belief that progressive disease carries a poor prognosis (Kurtzke, 1971; Poser *et al.*, 1982*b*; Verjans *et al.*, 1983). The quantitative implications of 'progressive MS', especially for reaching advanced disability, have been poorly defined. Clinicians conducting clinical trials are occasionally surprised at the favourable results in their control groups. For example, Nuwer *et al.* (1987) recently found that disability in a placebo-treated control group of MS patients with CP disease changed by a mean of 0.5 points on the DSS over 3 yrs of follow-up. This may be partly due to placebo effect inherent in participation in a clinical trial. However, exaggerated preconceptions of the clinical course in patients with progressive disease may be a factor. MS patients may progress slowly in terms of the DSS once DSS 6 is reached. We found that the mean rate of deterioration in the total population was only 0.5 DSS points per yr even in patients with progressive disease. While the DSS is an ordinal scale and the quantitative significance of this value is undefined, the rate of change on the DSS is a well accepted criterion for entry into clinical trials, and for monitoring drug effectiveness. This observation has great significance in selection of patients for such trials and in determining the length of follow-up.

The results of other series reporting outcome as disability indexed to duration of disease have been summarized recently (Weinshenker and Ebers, 1987). Results of the series of Panelius (1969) and Confavreux *et al.* (1980) are best compared with outcome of the Middlesex County group, those of McAlpine and Compston (1952) with outcome in our total population and those of Kurtzke *et al.* (1977) with outcome in the SO group, based on similarity of ascertainment of the study populations and methods of follow-up. The only previously reported life table analysis of disability is that of Confavreux *et al.* (1980), who reported that 8, 25 and 40% of his clinic population had reached the equivalent of DSS 6 at 5, 10 and 15 yrs from onset of MS, respectively; this compares with 14, 32 and 50% in our series. Substantial variation exists in the reported rate at which DSS 8 is reached (Weinshenker and Ebers, 1987), probably reflecting differences in follow-up.

Frequent references are made to the entity of 'benign MS' (McAlpine, 1961; Thompson *et al.*, 1986). The definitions used are arbitrary and, of necessity, retrospective. We propose a statistical definition based on the observed rate of progression of disability. For example, 10% of patients would still not have reached DSS 3 by 22 yrs or DSS 6 by 35 yrs; these figures provided a more rational basis for the definition of benign MS. The outcome of MS is a continuum between nonprogressive and rapidly aggressive disease. Longstanding, apparently benign, relapsing/remitting disease can terminate with very disabling progressive disease. Similarly, progressive MS may result in a very slow deterioration which may appear to arrest for years in terms of the DSS.

We have provided data on the observed rate at which disability develops after patients enter a progressive phase of their illness. These data are important for design of trials of immunosuppressive or other agents that are designed to alter the course of MS. They can be used to estimate the desired size of a study population to show a given degree of benefit at a predetermined level of power for clinical trials. Future reports will discuss the prognostic value of the early temporal course of MS as well as that of various clinical and demographic parameters which can be determined in the early years of disease.

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CHANGES IN EXCITABILITY OF HUMAN CUTANEOUS AFFERENTS FOLLOWING PROLONGED HIGH-FREQUENCY STIMULATION

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SUMMARY

Prolonged high-frequency stimulation of cutaneous nerves can result in paraesthesiae that begin 20 to 30 s after the end of the train and last for 5 to 10 min. In the present experiments the effects of such stimulation on the excitability of human cutaneous afferents and on their refractory and supernormal periods were measured to determine whether these changes could explain the postactivation paraesthesiae. Attention was focused on the axons of lowest threshold (1.0-1.5 T) in the compound sensory action potential evoked by stimulating the digital nerves of the index or middle fingers. Repetitive activation produced two opposing effects on the excitability of low-threshold cutaneous afferents. Following stimulus trains of short duration (1-5 min) the dominant effect was a long-lasting decrease in excitability, such that the amplitude of a test afferent volley was always less than before stimulation. With these trains, no subject experienced paraesthesiae. For 10 min after stimulus trains lasting longer than 7 to 12 min the dominant effect was an increase in excitability such that the amplitude of the test volley was greater than before stimulation. Within this interval, following such trains, subjects experienced paraesthesiae. The extent and duration of supernormality induced by a supramaximal conditioning stimulus were greatly increased by stimulation for 1 min. Following stimulation for 10 min, the degree of supernormality of the enhanced test volley was much the same as before stimulation, but was inappropriately high for the size of the test volley. The sum total of the excitability change and the change in supernormality resulted in a larger potential after stimulation, whether the train lasted 1 min or 10 min. It is concluded that the postactivation changes in axonal excitability could predispose the most excitable axons to generate ectopic impulses and, thereby, to produce paraesthesiae.

INTRODUCTION

The ability of an axon to conduct an impulse can be modified by its history of prior activity. A single impulse is followed by fluctuations in axonal excitability such that the axon initially becomes subexcitable in the absolute and relative

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refractory periods, then hyperexcitable in the supernormal period and finally subexcitable again in the late subnormal period. These changes in axonal excitability can be demonstrated in compound sensory action potentials in human subjects (Gilliatt and Willison, 1963; Buchthal and Rosenfalck, 1966; Hopf *et al.*, 1976; Stöhr, 1981*a*, *b*; Stöhr *et al.*, 1981; Ng *et al.*, 1987) and in single human motor axons (Bergmans, 1970, 1973). Activation of an axon at high frequency is followed by profound subexcitability, the extent of which depends on the rate and duration of the stimulus train (e.g., Gasser, 1935; Bergmans, 1970; Schoepfle and Katholi, 1973; Raymond, 1979; Bostock and Grafe, 1985). Paradoxically, however, prolonged repetitive stimulation of sensory fibres can induce paraesthesiae (Bergmans, 1970, 1973; Ochoa and Torebjörk, 1983; Ng *et al.*, 1987), and similar stimulation of motor axons can induce fasciculation (Bergmans, 1970, 1982).

In many conditions affecting the peripheral nerves, paraesthesiae result from ectopic impulse generation in pathological axons (Lance *et al.*, 1979; Ochoa and Torebjörk, 1980, 1983; Nyström and Hagbarth, 1981; Nordin *et al.*, 1984; for reviews, *see* Culp and Ochoa, 1982; Hagbarth *et al.*, 1984; Rasminsky, 1984). Similarly, the paraesthesiae that result from high-frequency repetitive stimulation of sensory fibres could result from ectopic foci in the stimulated axons, in which case they could constitute a good model for the pathological conditions. Ectopic impulses would be expected to arise from axons rendered hyperexcitable by their repetitive activity and, indeed, Ng *et al.* (1987) reported a postactivation increase in axonal excitability for human sensory fibres. This finding has no precedent in previous literature, the dominant effect of repetitive activation being subexcitability in all studies, reptilian, mammalian or human (Gasser, 1935; Bergmans, 1970, 1982; Schoepfle and Katholi, 1973; Raymond, 1979; Bostock and Grafe, 1985).

In order to resolve the apparent conflict between the results of Ng *et al.* (1987) and the established literature, the present experiments were undertaken to examine in detail the effects of repetitive stimulation at high frequency on human sensory axons. Such stimulation was found to produce two opposing changes in axonal excitability, a long-lasting subexcitability on which is superimposed a transient hyperexcitability, the resultant effect dependent on the duration of the conditioning stimulation and the elapsed time from the end of stimulation. Changes in the refractory and supernormal periods have also been documented.

METHODS

Twenty-six experiments were performed with informed consent on 7 healthy volunteers. The digital nerves of the index or middle finger were stimulated using two ring electrodes around the proximal phalanx. The resulting sensory action potential was recorded at the wrist by a subdermal needle electrode placed over the median nerve with a reference 3–4 cm laterally. The finger was isolated by nonconductive material to prevent stimulus spread. Following electrode placement the hand was draped over a cotton-covered cylinder and the entire arm and hand were wrapped in a cotton blanket. Temperature was measured with a thermocouple at the stimulating and recording sites and was maintained constant between 31-34° C throughout all experiments. Subjects were asked to keep the arm immobile while they remained in a comfortable seated position with arms propped on a padded table. A 2 wk interval was allowed between experiments on the same finger in order to avoid cumulative effects of stimulation.

Two constant current units connected by a diode bridge were independently controlled by a Grass S88 stimulator through two stimulus isolation units. The stimuli consisted of square-wave pulses of 0.1 ms duration delivered singly or in pairs at a rate of 1 Hz. The conditioning stimulus (S1) was set at maximum for the nerve volley and was delivered through the first constant current unit. The test stimulus (S2) was delivered through the second constant current unit at an intensity that produced a potential approximately one-third of maximum (*see* fig. 1). Eight sets of averages of 16 test potentials were recorded in order to establish the variability of the control The current setting for S2 was not altered for the remainder of the experiment in order to ensure stability of the stimulus. S2 was delivered alone for investigations of changes in axonal excitability following high-frequency stimulation, or with S1 in a conditioning-test paradigm in studies of changes in the recovery cycle following a single (S1) stimulus. For each experiment a train of impulses with a frequency of 200 Hz was given through the S1 stimulator for 1-12 min at an intensity maximal for the nerve volley. The amplitude of the action potential was monitored throughout the stimulus train and current was increased as necessary to maintain an amplitude of at least 80% of control in order to ensure participation of most large myelinated fibres.

Sensory action potentials were recorded on an averager with 512 bins and a sampling rate of 25 or 17 kHz for a 20 or 30 ms sweep, respectively. For each recorded potential, 16-32 sweeps were averaged and analysed on-line or stored on computer disc for subsequent analysis. Amplitudes and latencies were measured using cursors. Amplitudes were measured from the initial positive peak to the subsequent negative peak Latencies were measured from the onset of the stimulus artefact to the first positive peak and the first negative peak.

In the present studies changes in the 'excitability' of cutaneous afferents were measured by changes in the amplitude of the test volley evoked by a single submaximal stimulus (S2). The 'recovery cycle' plots the effects of a preceding supramaximal stimulus (S1) on the excitability of cutaneous afferents using different conditioning-test intervals. 'Supernormality' and 'subnormality' were present when the amplitude of the conditioned test potential was respectively greater or less than the amplitude of the unconditioned test potential.

Sixteen experiments examined the changes in excitability of cutaneous afferents as reflected by changes in the amplitude of response to a fixed stimulus after stimulus trains of different durations. The test potential was measured before and at 1 min intervals for 15-60 min after the end of the stimulus train. Each amplitude obtained subsequent to the stimulus train was compared with the pretrain value and plotted as a percentage of control.

The recovery cycle of the nerve following a supramaximal conditioning stimulus was studied before and after repetitive activation in 12 experiments. For 8 of these, S2 was conditioned by S1 using intervals of 3, 5, 7, 10, 15, 20 and 25 ms. Averages were obtained of the unconditioned and conditioned test potential prior to the train and each 10 min after the train. Of necessity this testing sequence took 8 min to complete, and was therefore performed on a background of changing axonal excitability. In the other 4 experiments a single conditioning-test interval (5 ms) was followed each minute for 1 h after the stimulus train.

For all experiments the subjects were asked to report the presence or absence of paraesthesiae and to note the location, intensity and duration of any sensory symptoms. The subjects were periodically questioned and any subjective positive symptoms were noted Formal sensory testing was not done in order to avoid external stimuli that might alter the normal pattern of excitability change or disturb the recording electrodes.

RESULTS

Paraesthesiae following long periods of repetitive activity have been reported by Bergmans (1970, 1973) for a single digital nerve that was involved in a tetanus at 300 Hz applied to a motor fibre. A previous study from this laboratory (Ng *et al.*, 1987) found that paraesthesiae developed after repetitive stimulation at 200 Hz for 10 min. For the present 26 experiments the digital nerve was stimulated maximally at 200 Hz for 1-12 min. During the stimulation most subjects reported intense tingling throughout the digit with some discrete punctate sensations. In 6 experiments on 3 subjects no paraesthesiae were noted following a 1 min stimulus train. One subject reported no positive sensations following trains of 3 and 5 min duration. The same subject reported that paraesthesiae began within 30 s of a 7 min train and then gradually waned over approximately 10 min. For all 17 experiments in which the repetitive stimulation lasted 10 or 12 min, the subjects reported paraesthesiae within 30 s of the end of the train. The paraesthesiae were most intense in the first minute and were confined to the finger that was stimulated. Test stimuli were often reported to trigger an increase in the paraesthesiae or to evoke a brief vibratory sensation. The paraesthesiae subsided gradually over 5-10 min. At 30-40 min after the train, the subjects often reported a warm numb sensation in the finger.

Size of the test potential

The relation between stimulus current and the amplitude of evoked sensory action potential was studied in 15 experiments by varying the stimulus over 8-15 current settings from that required to produce a discernible potential (approximately 1 μV) to supramaximal. These data were used to set the level of the test stimulus for the subsequent components of these 15 experiments. The error bars in fig. 1 indicate that the test potentials had a mean amplitude of 38.5% of maximum (SD 6.6%), and required a stimulus 1.35 times threshold (SD 0.12). In the remaining 11 experiments the test stimulus was set by trial-and-error such that it was 39.8% (SD 7.1) of maximum. It is therefore probable that, in all 26 experiments, the test stimulus (S2) was in the range 1.1-1.5 times threshold for the first recruited axons and activated only the lower-threshold axons of the large myelinated fibre range. The mean latency of the test potentials was 2.54 ms (range 2.24-2.80 ms); the latency of the maximal potential 2.50 ms (range 2.24-2.64 ms).

Changes in nerve excitability

A 1 min stimulus train decreased the excitability of digital afferents as reflected by a fall in the amplitude of the test potential (fig. 2). Following the train the average amplitude fell to 39% of its control value (range 8-64%) for 6 experiments in 3 subjects. The response to S2 returned to control levels by 20 min. This is consistent with previous studies on motor and sensory fibres in animals and man (Gasser, 1935; Bergmans, 1970; Raymond, 1979; Bostock and Grafe, 1985), studies

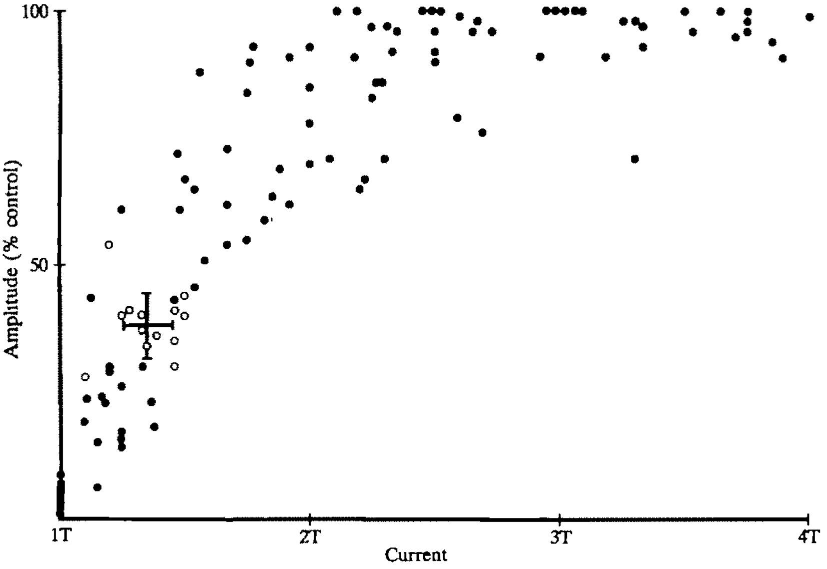

FIG. 1. Stimulus response relationship of the compound sensory action potential Pooled data from 15 experiments. The test potentials and the test stimuli (S2) required to elicit them are indicated by open circles. The error bars illustrate the mean ±1 SD The mean test stimulus (S2) was 1.35 times threshold for the first recruited axons (SD 0 12). This stimulus elicited test potentials of mean amplitude 38 5% of maximum (SD 6.67%)

that have invariably shown a rise in the threshold for electrical activation following repetitive stimulation.

Repetitive stimulation for 10 min resulted in a consistent increase in axonal excitability for 10 min following the stimulus train (fig. 3). Thirty seconds after the train ended, the amplitude of the test potential was well above its pretrain control reaching a maximal value of 145% of control (range 124-178%, 6 subjects) over 2-5 min. The amplitude then fell to a nadir of 14-59% of control by 30 min in the 3 subjects followed for 1 h. In an additional 6 experiments devoted primarily to changes in the supernormal period (*see* later), the amplitude of the unconditioned test potential was increased to 119-191% of control in the early posttrain period, but then fell to control levels more gradually than in fig. 3, when S2 was delivered without a supramaximal conditioning volley. Presumably the supramaximal (S1) stimulus used in the latter 6 experiments for supernormality determinations interfered with the true evolution of the late changes in excitability. The increase in excitability was found in all subjects and confirms previous work from this laboratory (Ng *et al.*, 1987).

The appearance of the postactivation increase in excitability was studied using stimulus trains of different duration (fig. 4). Only with the 7 min and 10 min trains was the amplitude of the test potential increased above the control level, but with the 3 min and 5 min trains the postactivation depression appeared to mask an early but weak increase in axonal excitability. This phenomenon can also be seen

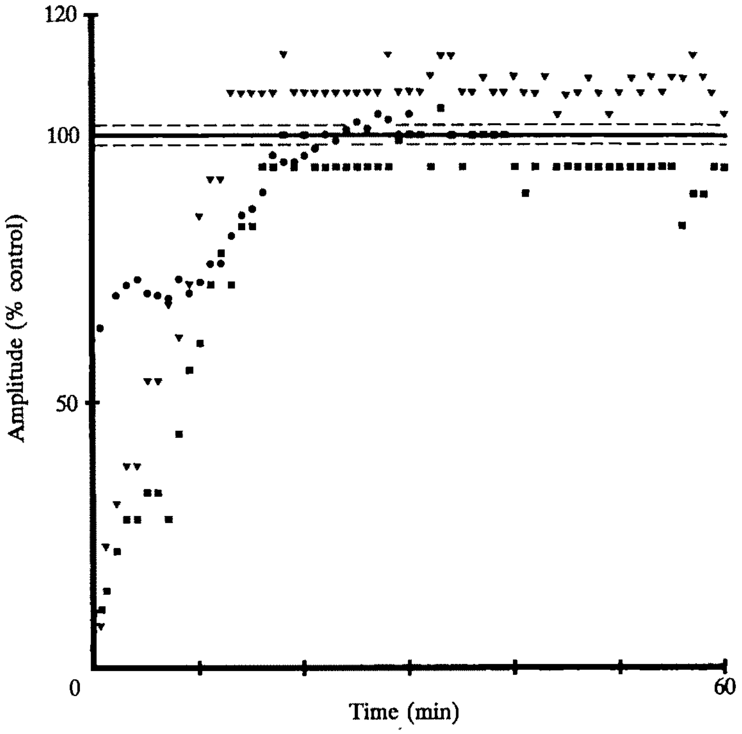

FIG 2 Changes in amplitude of the test potential following repetitive activation 1 min. Data for 3 subjects for one of the two experiments on each subject. The dashed lines represent the variability of the test potential before tetanization, assessed for each subject using 8 consecutive averages of 16 responses. Note that a transient increase in excitability is superimposed on the more profound postactivation depression for the subject illustrated by the circles

in fig. 2 for a second subject (filled circles), in this case after stimulation for 1 min. The early postactivation enhancement of excitability increased with the duration of the train. The second phase of postactivation depression also became more profound with increase in train duration. The test potential regained control amplitude by 30 min after a 1 min or 3 min stimulus train, but was still depressed at 60 min for the longer trains (89%, 71% and 87% of control for trains of 5, 7 and 10 min, respectively).

To verify the excitability changes reported above, a different experimental paradigm was used in a single experiment to follow the excitability in a population of fibres. A sensory potential 34% of maximum was stored on the averager as a template and at each minute after stimulation for 10 min the current required to achieve the same amplitude was measured. The 10 test potentials were stored and it was subsequently confirmed that they approximated the desired size (within 95–110% of the template). This 'constant-amplitude' paradigm yielded comparable results to the 'constant-stimulus' paradigm: 1 min after the 10 min train the current required to produce a test potential of control amplitude was reduced to 68% of

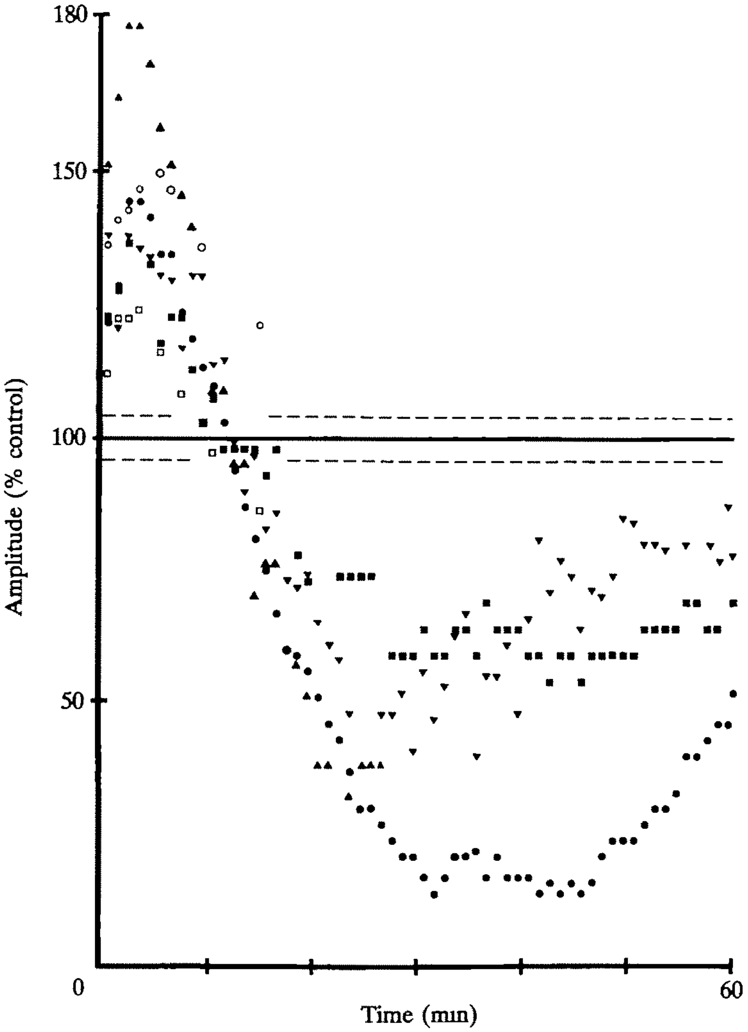

FIG 3. Changes in amplitude of the test potential following repetitive activation for 10 min. Data for 6 subjects, 3 of whom were followed for 1 h The dashed lines illustrate the variability of the test potential before stimulation, as for fig. 2. The experiment plotted using upright triangles was performed using different electrodes for the stimulus train and the test stimuli, proximally and distally around the digit, respectively.

the pretrain value. Over the ensuing 9 min, the required stimulus current gradually increased towards the control level.

In 3 experiments, in order to study a wider spectrum of fibres in digital nerve, the amplitude of the sensory action potential was measured at various current levels from subliminal to supramaximal before and after repetitive stimulation for 10 min. Threshold was reduced in the early posttrain period such that the current needed to produce a discernible potential fell from 10 mA (pretrain) to 5-6 mA (posttrain). The stimulus levels that had evoked a threshold potential before

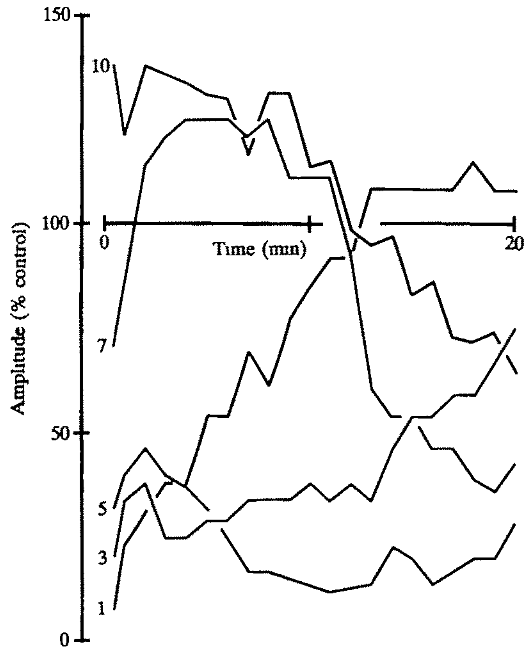

FIG. 4. Changes in amplitude of the test potential following repetitive activation for 1, 3, 5, 7 and 10 min. Data from different experiments on the same subject.

repetitive stimulation resulted in potentials that were 250%, 287% and 350% of control. The smaller the test potential the greater the degree of potentiation after the train (fig. 5). These findings provide a third paradigm demonstrating that the excitability of the low-threshold fibres (1.0–1.5 T) in the sensory action potential is enhanced immediately after repetitive activation for 10 min.

It is probable that different axons did not undergo identical changes in excitability. Immediately after the stimulus train, a stronger stimulus was required to produce a maximal potential and even then the control amplitude could not be achieved. Current was increased up to three times the level previously required without restoring maximal amplitude to its pretrain value. This finding could be due to profound posttrain hypoexcitability of the highest threshold fibres (as has been demonstrated to occur with human cutaneous afferents subjected to repetitive activation; *see* Torebjörk and Hallin, 1974; Mackenzie *et al.*, 1977). Alternatively, it could reflect a change in the dispersion of the compound sensory action potential due to unequal changes in latency of individual axons, or could result from a decrease in the size of constituent single-fibre potentials making up the compound action potential. Spontaneous ectopic discharges induced in some axons by repetitive stimulation might also have diminished maximal amplitude because of occlusion between the ectopic impulse and the electrically evoked impulse. On the other hand, the amplitude of the maximal potential exceeded the control amplitude some 30 min after the train. This finding has three possible explanations. First, the control nerve volley may not have been truly maximal. Secondly, dispersion of different fibres in the compound potential might have decreased due to unequal latency shifts as axonal excitability changed. Finally, the amplitude of single fibre action potentials could have been altered by the repetitive stimulation. Changes in the maximal compound sensory action potential

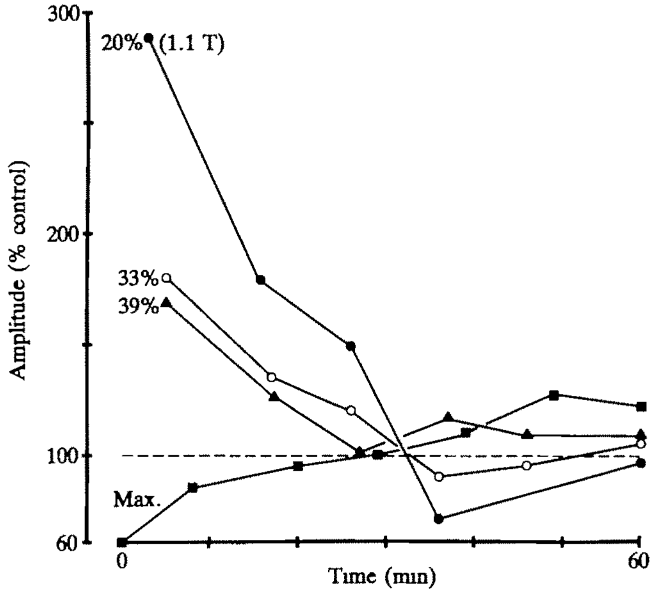

FIG 5 Changes in test potentials of different control amplitudes following repetitive activation for 10 min. Four control amplitudes were chosen. 20%, 33%, 39% and 100% of maximum The smallest control potential (20%) was evoked by a stimulus 1 1 times threshold for the first recruited axons.

were seen under other circumstances: during repetitive stimulation amplitude fell, usually to about 80% of control, despite increases in stimulus current of 10–20 mA. In addition the conditioning volleys used to chart posttrain changes in supernormality were commonly smaller in the immediate posttrain phase and larger later after the train (at 30–40 min). It should be stressed that changes in the maximal potential occurred in the opposite direction to those of the smaller test potential and cannot account for the excitability changes documented for low-threshold fibres.

The changes in excitability were not the result of local changes at or beneath the stimulating electrodes. In 2 subjects, the stimulus trains were delivered as usual, at the proximal phalanx, but excitability was tested using a second set of ring electrodes around the distal phalanx. The pattern of amplitude change following the train was not altered. Data for one of these experiments are included in fig. 3 (upright triangles) and for the other in fig. 8. In an additional experiment the stimulus train was administered at the distal phalanx while the test stimulus was given at the proximal phalanx. In the first 5 min following the train the amplitude of the test potential reached 191% of its pretrain control.

The latency of the compound sensory action potential was altered by repetitive stimulation. Immediately following repetitive stimulation for 10 min, the latencies to the first positive and negative peaks of the maximal potential were prolonged by, on average, 0.06 ms (2.7%) and 0.08 ms (2.6%), respectively. The latencies for the test potential were increased by 0.08 ms (3%) and 0.17 ms (5.2%). Following repetitive stimulation for 1 min there were similar changes in latency. Following the 10 min train latency gradually decreased until, 40 min after the train, the positive and negative peaks of the test potential occurred, on average, 0.13 ms (5.5%) and 0.12 ms (3.8%) earlier than control, respectively. This decrease in latency could not have been due to effective shortening of the conduction distance because the amplitude of the potential was near or below control at that time.

Changes in the refractory and supernormal periods

Following an impulse, an axon is initially absolutely and then relatively refractory to a second stimulus, but it then passes into a supernormal phase and finally a late subnormal phase before it recovers the control excitability. The recovery cycle of compound sensory potentials following a supramaximal conditioning stimulus (S1) contains comparable phases. The refractory and supernormal periods were studied before and after repetitive stimulation, using a fixed submaximal test stimulus (S2), delivered alone and after S1, at conditioning-test intervals of 3, 5, 7, 10, 15, 20 and 25 ms. Before the train, and every 10 min after for 60 min, 16 potentials were averaged in response to the unconditioned S2 and each conditioning-test (S1-S2) pair.

Fig. 6 illustrates the change in the recovery cycle after a 1 min train, testing beginning immediately after the train and finishing 8 min later. After repetitive activation the supernormal period began earlier and was prolonged in duration.

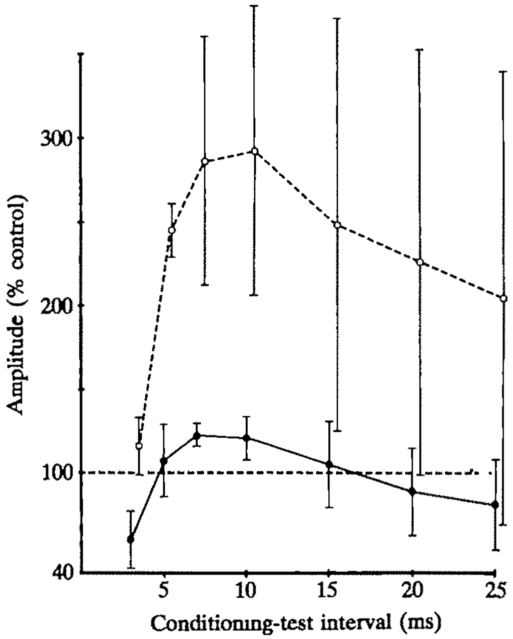

FIG 6. Changes in supernormality immediately after repetitive activation for 1 min. Each graph shows the changes in amplitude of a test potential following a supramaximal conditioning stimulus, using conditioning-test intervals of 3, 5, 7, 10, 15, 20 and 25 ms Data obtained before stimulation: filled circles, and after stimulation: open circles. The postactivation data has been plotted slightly to the right of the preactivation data to avoid overlapping. Each data point shows mean and SD for data from 3 subjects

At the 3 ms conditioning-test interval prior to the train, the amplitude of the test potential was, on average, 60% of its control, but in the early posttrain period the test potential was 116% of its unconditioned control. The peak of the supernormal phase (286%) occurred at the 10 ms conditioning-test interval and supernormality was still present 25 ms after the conditioning stimulus. It should be noted that these changes in refractoriness and supernormality are expressed as a percentage of the unconditioned test potential, the size of which was affected by the stimulus train (as in fig. 2). Of necessity a separate unconditioned test potential was measured for each interval in the recovery cycle. The unconditioned test potential regained its control amplitude 20 min after the train, but the degree of supernormality was still potentiated significantly at the shorter intervals until 40 min after the train.

The recovery cycle did not appear to be altered significantly in the early period (the first 8 min) after repetitive stimulation for 10 min (fig. 7). However, after stimulation the unconditioned test volley was bigger than before it (*see* fig. 3), and normally the degree of supernormality is inversely related to the size of the test potential when the present paradigm is used (Ng *et al.*, 1987). As the unconditioned test potential became smaller than control (*see* fig. 3), the extent of supernormality exceeded the pretrain values, the greatest potentiation of supernormality occurring 50–60 min after the train. Thus, taking into account the larger unconditioned test volley in the first 10 min after repetitive stimulation, the degree of supernormality was potentiated at all stages following the 10 min train.

To determine whether the combined changes in excitability and supernormality could result in a larger compound action potential as postulated by Ng *et al.* (1987), the conditioned potentials were compared before and after repetitive stimulation for 1 min and 10 min. Immediately following the 1 min train, the mean amplitudes of the conditioned potentials at the 5 ms conditioning-test interval were 100–128% of their pretrain values. Immediately after the 10 min

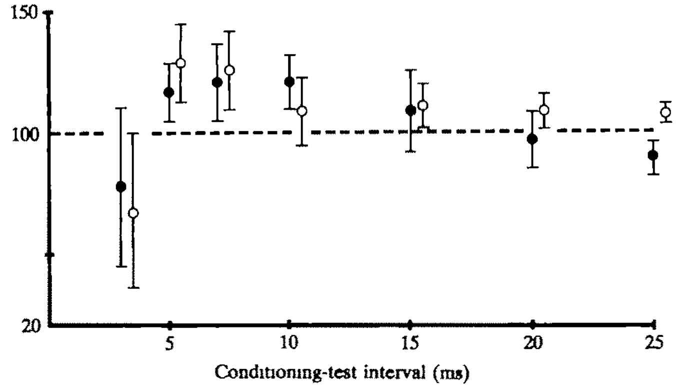

FIG. 7 Changes in supernormality immediately after repetitive activation for 10 min Similar format as for fig. 6. Each data point shows mean and SD for data from 5 subjects.

train the mean amplitudes of the conditioned potentials at the same interval were 110–151% of the pretrain conditioned values.

It took 8 min to collect the data for figs 6 and 7. The recovery cycles do not reflect the situation at a single instant in time, but they do indicate the distortion of the cycle produced by the stimulus trains. In order to clarify the relationship between the excitability changes and the alterations in supernormality that follow repetitive activation, a single conditioning-test interval was followed: S2 was delivered alone and 5 ms after S1, each minute for an hour following stimulation for 3, 5, 7 and 12 min. The data from the last of these experiments are illustrated in fig. 8. Before stimulation, the nerve was relatively refractory at the 5 ms interval, with the amplitude of the conditioned test potential only 1.9 μV (38%) of the unconditioned control (5 μV). Following the train, supernormality was present at the 5 ms interval and this persisted for the entire hour. The fluctuations in excitability of the unconditioned test potential and in supernormality were reciprocal in all 4 of these experiments (*see* fig. 8) and also in a fifth experiment in which stimulus current was varied to produce a test potential of fixed amplitude. In

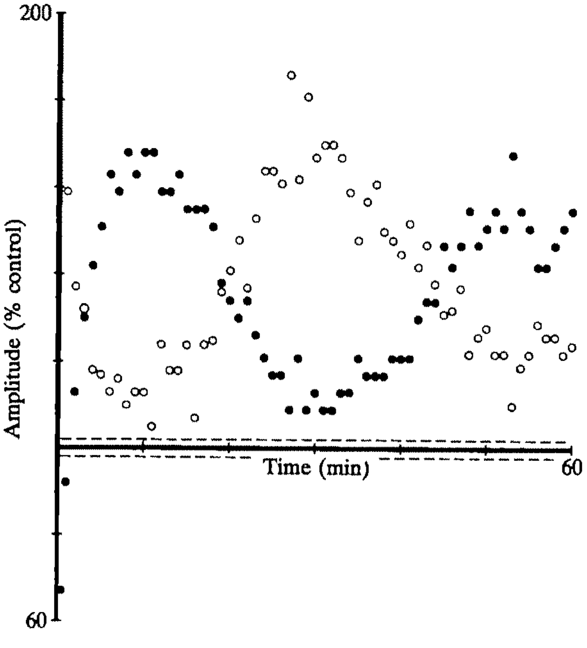

FIG. 8. Reciprocal relationship between the change in excitability and the degree of supernormality following repetitive stimulation for 12 min. The variability of the test potential before stimulation is indicated by the dashed lines about the 100% level. The evolution of the changes in excitability (filled circles) was determined by the amplitude of the unconditioned test potential evoked by a constant test stimulus (S2). The degree of supernormality was measured at the 5 ms conditioning-test interval (open circles) and is expressed as a percentage of the amplitude of the unconditioned test potential (filled circles) In this experiment separate electrodes were used for the stimulus train and for the subsequent conditioning and test stimuli, the former proximal around the digit, the latter distal.

fig. 8, the potentiation of supernormality was greatest 27–33 min after the train at a time when the unconditioned potential was close to its control amplitude. This time course of enhanced supernormality differs slightly from that found when the full recovery cycle was plotted (*see* earlier), presumably due to the different stimulus paradigms, but with both paradigms the degree of supernormality was enhanced following prolonged repetitive stimulation. In fig. 8 the amplitude of the conditioned potential ranged from 7.0 μV (immediately after the train ended) to 9.6 μV (at 27 min), equivalent to 368–505% of the pretrain conditioned amplitude (1.9 μV).

DISCUSSION

These results indicate that a short period of high-frequency activation (1–5 min) decreases excitability in human sensory fibres, much as it does in animals (Gasser, 1935; Raymond, 1979) and in human motor fibres (Bergmans, 1970). Longer stimulus trains (7–12 min) induce a transient hyperexcitability, during which the test potential is increased in amplitude, threshold is reduced, and the subject develops paraesthesiae. The degree of supernormality that follows a single impulse in normal nerve is potentiated during the hypoexcitable state that follows brief trains, and preserved despite the hyperexcitability after longer trains.

The basic paradigm used in the present study of measuring changes in amplitude in response to a fixed stimulus has been used by other authors as an indication of axonal excitability during the recovery cycle following activity (Gilliatt and Willison, 1963; Seneviratne *et al.*, 1972; Stöhr, 1981*a*; *see also* Ng *et al.*, 1987). Stöhr found that the magnitude of supernormality and subnormality were greater when expressed as amplitude ratios than as threshold ratios, but that the temporal profiles were identical for the two methods. This would be expected because the slope of the current-amplitude curve near threshold (1–2 T) is steep, so that a relatively small increase in stimulus strength evokes a large change in amplitude (*see* fig. 1). Amplitude change to a near-threshold stimulus may therefore be more sensitive than threshold change as a measure of excitability.

The use of a compound action potential to follow changes in excitability does have two limitations. First, the compound potential will reflect the net change in excitability of a population of axons and could not reveal conflicting excitability changes in different axons (*see* next section). Secondly, changes in dispersion of the compound potential will affect its amplitude. In the present study the measurable increases in latency and dispersion were small and were similar with 1 min and 10 min trains. An increase in dispersion cannot account for the increase in amplitude seen following prolonged trains. In addition, the increase in excitability following prolonged trains was confirmed using three different experimental paradigms, including measurements of threshold of the first-recruited axons. It can be concluded that the limitations of compound action potentials do not affect the validity of the present results.

Mechanisms of the excitability changes

Using frog sciatic nerve, Gasser (1935) established that, during the slow positive after-potential (P2) following repetitive activation, the excitability of low-threshold axons is reduced. Raymond (1979) found that this postactivation depression did not occur when ouabain was administered, implying that it resulted from an electrogenic sodium pump. The time course of P2 was later correlated with intracellular hyperpolarization seen after repetitive activation (Barrett and Barrett, 1982). When the hyperpolarization was eliminated by cooling or treatment with ouabain, Barrett and Barrett (1982) found that the stimulus train was followed by a slow depolarizing after-potential, the magnitude of which increased with the frequency and duration of the train. When lithium is used to block the sodium pump, repetitive activation results in axonal depolarization and a decreased axonal threshold in both nonmammalian (Schoepfle and Katholi, 1973) and mammalian axons (Bostock and Grafe, 1985; *see also* Ritchie and Straub, 1957). The depolarization seen during pump inactivation appears to be largely passive, due to extracellular potassium accumulation (Schoepfle and Katholi, 1973; Connors *et al.*, 1982), and this mechanism has been invoked to explain the increase in excitability seen in cerebellar parallel fibres when an adjacent row is subjected to a stimulus train (Kocsis *et al.*, 1983).

From the above data, repetitive activation has complex effects on axonal excitability, involving at least two different and antagonistic phenomena, active and passive, and that excitability at any one time reflects the balance of these phenomena (*see* Schoepfle and Katholi, 1973). To explain an increase in axonal excitability as seen in the present study does not necessarily require a phenomenon unique to human cutaneous afferents. The remarkable finding of the present study, confirming and elaborating the suggestions of Ng *et al.* (1987), is not that there may be a postactivation increase in excitability, but that this increase can dominate the better documented postactivation depression.

There is an alternative explanation for the increase in excitability: ectopically-firing axons with enhanced supernormality will generate a greater response to the test stimulus when the stimulus is delivered during the supernormal period that follows an ectopic impulse. Three results militate against this explanation. (1) The apparent increase in excitability would be dependent on enhanced supernormality, and should be greater following those trains that produced greater increase in supernormality. The 1 min trains produced greatest increase in supernormality but were never followed by paraesthesiae or an enhanced test potential. (2) The apparent increase in excitability would be dependent on ectopic neural activity and would be immediately replaced by profound subexcitability when the ectopic firing (and paraesthesiae) ceased. Correlation of the time course of the paraesthesiae (*see* p. 150) with fig. 3 suggests that this is not so. (3) As judged by the discrete nature of the paraesthesiae, the number of ectopically-firing axons is likely to be small, insufficient to produce an increase of the test potential by 50% (and sometimes more). Of the two explanations for the enhanced excitability, this alternative explanation seems less likely than that advanced in the preceding two paragraphs and, as discussed above, there is some experimental precedent for the preferred explanation.

Given that two opposing phenomena can affect the excitability of cutaneous axons subjected to prolonged high-frequency stimulus trains, an apparent conflict between the present results and earlier findings from this laboratory can be resolved. Ng *et al.* (1987) reported that 2 subjects experienced paraesthesiae when the test potential was only 88% and 73% of the prestimulation control. The stimulation sequence consisted of repeated trains of increasing duration separated by 1 min, the paraesthesiae appearing after cumulative totals of 11.5 min and 16.5 min, respectively. In both cases, the amplitude of the test potential had been more severely affected by the earlier trains, being 8% after the 30 s train and 62% after the 3 min train, respectively. Since the active pump-dependent depression of axonal excitability is greater the longer the stimulus train, the longer trains must have produced an opposing excitability change that affected some cutaneous afferents, even if it was insufficient to generate a larger compound test potential. The findings of Ng *et al.* can be explained if the two opposing influences on excitability affect different axons differently. Indeed it is also probable that different parts of the same axon undergo different excitability changes and that the generation of ectopic impulses therefore occurs only at specific foci of greatest excitability. It is concluded that the findings of Ng *et al.* (1987) do not conflict with the present study; instead they indicate a limitation of the use of compound potentials to measure excitability when opposing processes can affect the excitability of individual axons in a non-uniform manner.

Mechanisms involved in supernormality

In nonmammalian species, the refractory period has been attributed to inactivation of sodium conductance during high membrane conductance for potassium associated with repolarization (Raymond, 1979). In mammalian nodes, active potassium changes are confined largely to the paranodal and internodal membrane, and repolarization depends on a leakage current, not a specific increase in potassium permeability (Chiu *et al.*, 1979; Brismar, 1980). Supernormal excitability during the negative after-potential (Gasser, 1935) was found by Barrett and Barrett (1982) to correlate with an intracellular depolarizing after-potential, the behaviour of which was consistent with a passive electrical property of myelinated axons (*see also* Bostock and Grafe, 1985). Supernormality is potentiated during the hyperpolarization that follows repetitive activation (Gasser, 1935; Raymond, 1979; Bostock and Grafe, 1985), as it was here. A decrease in supernormality has been found during tetanization in the presence of cooling (Barrett and Barrett, 1982) or lithium chloride (Bostock and Grafe, 1985); both studies attributed this to the depolarization that coincided with extracellular potassium accumulation.

It may reasonably be asked whether the activity-dependent changes in the degree of supernormality are significant or whether they are merely measurement artefacts, of little clinical relevance, attributable to the background excitability change. Reciprocal changes in axonal excitability and the degree of supernormality are well documented in animal experiments (e.g., Bostock and Grafe, 1985), much as was found in the present study using compound potentials (*see* fig. 8). The marked increase in supernormality that followed brief stimulus trains was never associated with paraesthesiae, suggesting that enhanced supernormality is insufficient to produce ectopic impulse generation in the absence of axonal hyperexcitability (cf., however, results of Ng *et al.*, 1987, discussed in the previous section). In the present study, the degree of supernormality was similar before and after prolonged stimulus trains despite the greater size of the poststimulation test potential. Because the degree of supernormality is inversely related to the size of the test potential (Ng *et al.*, 1987), it is reasonable to conclude that the degree of supernormality is potentiated by repetitive stimulation regardless of train duration.

The combined increases in excitability and in supernormality should predispose the involved afferents to ectopic impulse generation. However, the consequences of enhanced supernormality can only become manifest after an impulse is generated in an axon. As suggested by Ng *et al.* (1987), the change in supernormality is unlikely to initiate ectopic impulses in an axon but it could help sustain an ectopic train once initiated and it could convert physiologically generated impulses into a bizarre self-perpetuating train.

Previous studies of repetitive stimulation in man

Bergmans (1970) studied single motor fibres in the median nerve in human volunteers and found consistent increases in threshold and latency following repetitive activation using short trains (5–10 pulses) or long trains (up to 30 min). He described two phases of depression, similar to those previously found by Gasser (1935): a brief (less than 200 ms) H1 phase following short trains, and a prolonged (15–60 min) H2 phase following longer trains. The H1 depression was sometimes followed by an increase in excitability. A phenomenon that may be comparable to the depression for motor fibres was described in sensory axons by Ochoa and Torebjörk (1983). After intraneural microstimulation at 100 Hz for several minutes they observed progressive conduction block in single afferents, but with longer trains single axons became spontaneously active.

The genesis of spontaneous discharges induced in single motor axons of human subjects by repetitive stimulation (300 Hz for 10–15 min) has been studied by Bergmans (1970, 1982). No evidence of increased axonal excitability was found, but excitability could not be measured directly (Bergmans, 1982, p. 405) and, instead, prolongation of latency and the changes induced by a brief train of stimuli were used as indirect measures of axonal hyperpolarization. It seems likely that these parameters were not measured in the critical 10–20 min immediately following the stimulus train (*see* fig. 20-5, Bergmans, 1982). In addition, a latency prolongation may not adequately measure net axonal excitability. In the present study, the latencies of test potentials were increased by a similar amount (3-5%) immediately after prolonged and brief stimulus trains. Some 40 min after 10 min trains, axonal excitability was profoundly depressed but latencies were shorter than their controls. We have no explanation for these latency changes but they do suggest that latency prolongation does not necessarily indicate depressed excitability, at least with the present experimental paradigm and possibly also with that of Bergmans (1982).

Using intrafascicular microstimulation of single cutaneous afferents, Ochoa and Torebjörk (1983) were able to induce ectopic firing after trains of 200-300 Hz for 5-10 min. The changes in excitability and supernormality documented in the present study would predispose the stimulated axons to the phenomenon demonstrated by Ochoa and Torebjörk (1983). However, studies comparable to theirs are required to demonstrate that this is so and to determine whether the subsequent long-lasting axonal hypoexcitability has perceptual consequences.

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CORPUS CALLOSUM SURGERY AND RECENT MEMORY

A REVIEW

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SUMMARY

A number of clinical reports have cited memory disturbances in surgical cases involving section of the corpus callosum This review, however, shows that persistent impairment of recent memory has tended to occur only in cases where there has been concurrent extracallosal damage, particularly to the fornix and its connections. Both the timing and sensitivity of psychometric tests as well as the availability of preoperative baselines are all important factors in determining the reliability of memory assessment following callosal surgery. A minimal delay of one year between surgery and final memory testing is needed because intellectual functions have been shown to improve markedly during the 12 months following callosal section. The use of discriminating psychometric tests with comparisons before and after operation is desirable, since global memory tests are relatively insensitive to disorders of recent memory.

INTRODUCTION

Surgical section of the corpus callosum is used to treat intractable epilepsy (Gazzaniga and LeDoux, 1978) and to provide surgical access to midline tumours (Jeeves *et al.*, 1979; Benes, 1982; Carmel, 1985). The reported consequences of complete callosotomy include disconnection in the visual (Levy *et al.*, 1972; Zaidel, 1979), auditory (Sparks and Geschwind, 1968; Springer *et al.*, 1978) and tactile (Geffen *et al.*, 1985) modalities, reduced imagination (Hoppe, 1977; Vilkki, 1981), difficulty with affective verbal expression (TenHouten *et al.*, 1985) and impaired recent memory (Zaidel and Sperry, 1974). This review focuses on reports of impairment of recent memory.

In one of the earliest clinical reports, Zaidel and Sperry (1974) assessed 8 patients with complete section of corpus callosum (including the anterior and hippocampal commissures) and 2 in whom the anterior two-thirds of the corpus callosum and the anterior commissure were sectioned. At least 3 years postoperatively, all patients showed Wechsler memory scale quotients (MQ; Stone

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and Wechsler, 1974) that were 13 to 25 points below their obtained Wechsler (1955) intelligence quotients (IQ). They also performed poorly on other standardized memory tests. Since IQ and MQ are positively correlated (0.8) in intact persons, these patients showed a specific impairment of memory. This finding was in agreement with the reports of close relatives. Zaidel and Sperry attributed the memory impairment to a loss of interhemispheric cooperation following commissural section. However, recent memory deficits of this type have been reported to occur with hippocampal damage in the absence of callosal section (*see* Woolsey and Nelson, 1975), and Zaidel and Sperry themselves noted that the callosotomy involved section of the hippocampal commissures and in some cases section of one or the other fornices connecting the hippocampi and mammillary bodies (*see* Huppert, 1981). Hence it is important to establish whether memory loss occurs in patients when extracallosal damage is minimal or absent.

For clinical purposes, memory is separated into three main components (Lezak, 1983): recent memory, involving memories stored within the last few hours, days, weeks or even months; remote long-term memory involving older events which may date from childhood; and immediate memory involving short-term memory which lasts, unrehearsed, for about 30 s. Diagnosis of recent memory loss is generally made following observational reports of memory difficulty and an MQ at least 1 SD (15 points) below the IQ value, which itself tends to remain stable in the presence of an acquired memory disorder.

With callosal section, it is important to consider the time interval between surgery and memory testing. Since intellectual functions have been shown to improve markedly during the first 6–12 months following callosal section (Lezak, 1983), memory impairment should have persisted for at least 1 yr postoperatively before a final diagnosis is made. On the other hand, magnetic resonance imaging has provided some evidence for secondary demyelination of callosal fibres following surgical section (Sussman *et al.*, 1987). Thus normal memory function during the first postoperative year may not necessarily be taken to indicate that dysfunction will not develop, as has previously been suggested (*see* Geffen *et al.*, 1980).

The following sections examine evidence for direct involvement of the corpus callosum in memory function. The first examines case reports in which only postoperative psychometric assessment of memory has been carried out; the second examines reports involving both preoperative and postoperative assessment; the third examines clinical reports in which psychometric analysis was absent; and the fourth considers pertinent animal work. Particular attention has been paid to whether memory loss may have been associated with damage to paracallosal structures, whereas reports of memory impairment based on measures taken less than 1 yr postoperatively have not been considered (e.g., Winston *et al.*, 1979; Bentin *et al.*, 1984).

LITERATURE REVIEW

Postoperative psychometric memory assessment

Fourteen case reports involving postoperative but not preoperative psychometric assessment of memory dysfunction have been located (*see* Table 1).

In the report by Zaidel and Sperry (1974), one subject (N.F.) had the anterior and hippocampal commissures partially sectioned, while the other (D.M.) had the left column of the fornix as well as the anterior commissures sectioned. Bentin *et al.* (1984) reported a case involving a small surgical lesion in the trunk of the corpus callosum and in which a postoperative memory deficit was indicated by a significant IQ-MQ difference. Memory loss in this case, however, may have been due to the effects of two ventriculoperitoneal shunts which had been used to treat normal pressure hydrocephalus or to radiotherapy (*see* Lezak, 1983), or to regrowth of the glioma which had been incompletely removed 2 yrs before assessment. Geffen *et al.* (1980) reported 1 subject (W.F.) with a recent memory deficit following section of the body of the corpus callosum, but which also involved bilateral section of the fornix. Campbell *et al.* (1981) reported 2 additional commissurotomy cases involving impairment in immediate auditory and/or visual memory. Both had had transections of the entire corpus callosum and the anterior and hippocampal commissures. In addition, one (J.M.) had sustained temporal lobectomy, and the other (W.J.) right frontal cerebral atrophy.

In all 14 cases listed in Table 1 there was damage to noncallosal structures or a complicating neurological condition which may have been related to the memory deficits measured. In addition to this, a further 8 cases have been reported in which callosal section involved only minor extracallosal damage and in which no memory dysfunction was detected (*see* Table 2). Two subjects received anterior callosal section (G.O.: Geffen *et al.*, 1980, Case 3: Bentin *et al.*, 1984), 1 had a posterior callosal lesion (Case 6: Bentin *et al.*, 1984); and 6 (Apuzzo *et al.*, 1982) had callosal incisions in the middle region of the corpus callosum.

Preoperative and postoperative psychometric memory assessment

Psychometric assessment both before and after callosal surgery provides the most rigorous test for callosal involvement in memory function. Reports of 10 such cases have been found (*see* Table 3). In only 1 case was there a measured fall in MQ following surgery (Case 5, Petrucci *et al.*, 1987) and this was restricted to a mere 8 points on the MQ scale. In 3 cases there were postoperative increases in MQ (D.H., LeDoux *et al.*, 1977; Cases 3, 4, Petrucci *et al.*, 1987). Four patients (Cases 1, 2, 3, 5, Petrucci *et al.*, 1987) who completed the more sensitive Auditory Verbal Learning Test (Taylor, 1959) demonstrated no postoperative loss in either immediate or delayed short-term recall or in the ability to learn word lists. One patient (M.K., Campbell *et al.*, 1981) demonstrated substantial postoperative loss (9 points) on the Benton Visual Retention Test (Benton, 1974) of visual memory, but this was complicated by the presence of right hemicerebral atrophy

TABLE 1 CASES OF CORPUS CALLOSUM LESIONS WITH PERSISTENT MEMORY IMPAIRMENT*

Case (sex)	*Lesion*	*Age at operation (yrs)*	*Clinical condition*	*Yrs postop.*	*IQ*	*MQ*	*Other memory assessments*
Zaidel and Sperry (1974)							
A A (M)	Complete section of CC, HC, AC	12	Ep	7.5	78	63	BVRT defective, MFD borderline, MSO average
C.C (M)	Complete section of CC, HC, AC	13	Ep.	7	72	58	BVRT defective, MFD borderline, MSO < average
L.B (M)	Complete section of CC, HC, AC	13	Ep	7	106	80	BVRT high average, MFD average, MSO average
R.M (M)	Complete section of CC, HC, AC	27	Ep	6	80	57	BVRT defective, MFD borderline, MSO defective
M K. (F)	Complete section of CC, HC, AC	29	Ep.	4.5	69	50	BVRT defective, MFD borderline, MSO < average
N G (F)	Complete section of CC, HC, AC, RF, MI	29	Ep	8.5	77	64	BVRT defective, MFD defective, MSO < average
N.W (F)	Complete section of CC, HC, AC, MI, partial damage to LF	35	Ep.	5.5	93	70	BVRT defective, MFD defective, MSO < average
R Y (M)	Complete section of CC, AC, HC	42	CHI/Ep	6	90	77	BVRT defective, MFD borderline, MSO defective
D M (M)	Partial section of CC, section of AC, damage to LF	23	CHI/Ep.	4	76	58	BVRT defective, MFD normal, MSO < average
N F. (F)	Section of anterior 2/3 CC, AC, HC	26	Ep	3.5	83	63	BVRT defective, MFD normal, MSO < average
Geffen *et al* (1980)							
W F (F)	Section of body of CC, section of LF, RF	14	III vent cyst	8	115	79	BVRT < average
Campbell *et al.* (1981)							
J.M (F)	Complete section of CC, HC, AC, temporal lobectomy	36	Ep	1 8	90 86	— —	BVRT defective BVRT defective
W.J (M)	Complete section of CC, HC, AC, right frontal cerebral atrophy	48	Ep	5	99	—	BVRT defective
Bentin *et al.* (1984)							
Case 1 (F)	15 mm incision in CC posterior to FM; right then left VPS, radiotherapy	25	Tumour blocking foramen of Monro	2	87	62	—

* Based on postoperative psychometric assessment in the absence of preoperative baselines Intelligence (IQ) and memory quotients (MQ) are shown, as well as the number of years after operation at which the patient was assessed. Full scale IQ unless otherwise stated Only impaired scores are shown F = female, M = male, AC = anterior commissure, CC = corpus callosum, HC = hippocampal commissure, LF = left fornix, RF = right fornix, MI = massa intermedia, RH = right hemisphere, VPS = ventriculoperitoneal shunt, AVM = arteriovenous malformation, CHI = closed head injury, Ep = epilepsy, III vent = third ventricle, AVLT = Rey Auditory Verbal Retention Test, BVRT = Benton Visual Retention Test, MFD = Memory-for-Designs Test, MSO = memory span for objects, MUS = Memory of Unrelated Sentences Test, STM = short-term memory, WMS = Wechsler memory scale

TABLE 2 CASES OF CORPUS CALLOSUM LESIONS WITHOUT PERSISTENT MEMORY IMPAIRMENTS*

Case	*Lesion*	*Age at operation (yrs)*	*Clinical condition*	*Yrs postop.*	*IQ*	*MQ*
Geffen *et al.* (1980)						
G O. (M)	Partial section of ant. CC, retraction of RH, minor RF damage	64	III vent. cyst	5	104	115**
Apuzzo *et al.* (1982)						
1	Incision in CC interforniceal (IF)	30	III vent. cyst	0	109	99
3	Incision in CC IF	26	Craniopharyngioma III vent.	0	97	114
5	Incision in CC IF	32	Cysticercosis III vent.	0	89	97
7	Incision in CC IF	49	Cysticercosis III vent.	0	86	81
8	Incision in CC IF	32	Cysticercosis III vent.	0	94	103
10	Incision in CC IF	33	AVM in foramen of Monro	0	80	91
Bentin *et al* (1984)						
3 (F)	Incision in ant. CC	38	III vent. cyst	2	122	117
6 (M)	Section of posterior CC	14	Cyst in posterior CC	0	94	89

* Based on postoperative psychometric assessment. Intelligence (IQ) and memory quotients (MQ) are shown, as well as the number of years after operation at which the patient was assessed. Full scale IQ unless otherwise stated. F = female, M = male, CC = corpus callosum, LF = left fornix, RF = right fornix, IF = interforniceal surgical approach, RH = right hemisphere, AVM = arteriovenous malformation, III vent = third ventricle.

** Other memory tests conducted yielded normal results.

and a left homonymous hemianopia, and was matched by a substantial (2 SD) fall in performance IQ. Five other patients (Cases 2–5, Petrucci *et al.*, 1987; D.M., Campbell *et al.*, 1981) who completed the sensitive Benton Visual Retention Test demonstrated no postoperative loss in visual memory.

Clinical reports

A number of reports in the literature have been based on clinical rather than psychometric assessment. The clinical studies also provide little support for callosal involvement in any memory dysfunction. Benes (1982), for example, reported 15 cases in which callosal section was performed in children for the treatment of cysts or tumours of the third ventricle or other midline structures. Although postsurgical loss of recent memory occurred in these cases, normal function generally returned after a period of 2 months. Carmel (1985) also reported a series of cases involving surgery for third ventricle tumours. Of 100 operations, 22 involved section of the corpus callosum, whereas 39 involved an alternative transcortical approach to the tumour and the remainder, a basal approach. Only 1 case each from the transcortical and the transcallosal groups presented with

TABLE 3. PATIENTS WITH PREOPERATIVE AND POSTOPERATIVE PSYCHOMETRIC ASSESSMENT*

Case	*Lesion*	*Age at operation (yrs)*	*Clinical condition*	*Yrs postop*		*Memory assessment*	
						Preop	*Postop.*
LeDoux *et al* (1977)							
D H	Complete section	15	Ep	0	IQ	92	103
(M)	of CC				MQ	93	108
					VSM	19	29
					MFD	3 errors	1 error
Campbell *et al* (1981)							
M.M.	Complete section	29	Ep	1.7	VIQ	89	86
(F)**	of CC, HC, AC, R				PIQ	88	60
	cerebral atrophy				BVRT (C)	10	1
	and left homonymous						
	hemianopia						
D.M	Frontal commissuro-	23	CHI/ep	7.6	IQ	76	73
(M)**	tomy; postop. seizures				BVRT (C)	8	6
Bentin *et al.* (1984)							
4	Incision in ant CC	35	III vent. cyst	0	IQ	114	115
(F)					MQ	118	116
Wale and Geffen (1986)							
W Y.	Section of ant. CC	61	opaque mass in	0	PIQ	110	106
(M)			region of foramen		MQ	125	121
			of Monro				
Petrucci *et al* (1987)							
1	22 mm opening in	43	Ep , III vent	0	MQ	143	143
(F)	body CC		cyst		AVLT (A5)	15	15
					AVLT (B1)	7	7
					AVLT (A6)	8	12
2	16 mm opening in	45	III vent	0	IQ	108	109
(?)	body CC		tumour		MQ	-	103
					AVLT (A5)	5	8
					AVLT (B1)	5	6
					AVLT (A6)	2	5
					BVRT (C)	5	6
					BVRT (E)	5	5
3	33 mm opening	42	III vent oligo-	0	IQ	99	106
(F)	in body CC		dendroglioma;		MQ	96	110
			hydrocephalus		AVLT (A5)	12	14
					AVLT (B1)	5	5
					AVLT (A6)	13	11
					BVRT (C)	5	7
					BVRT (E)	7	5
4	22 mm opening in	58	III vent. cyst	0	IQ	84	81
(M)	body CC				MQ	87	96
					BVRT (C)	4	4
					BVRT (E)	1	1
5	15 mm opening in	19	III vent oligo-	0	IQ	117	123
(?)	body CC		dendroglioma, left		MQ	115	106
			sided paresthesias		AVLT (A5)	14	15
					AVLT (B1)	4	9
					AVLT (A6)	9	13
					BVRT (C)	8	10
					BVRT (E)	2	0

* Intelligence (IQ) and memory quotients (MQ) are shown, as well as the number of years after operation at which the patient was assessed. Full scale IQ unless otherwise stated. F = female, M = male, CC = corpus callosum, Ep. = epilepsy, III vent. = third ventricle, PIQ = performance intelligence quotient, MFD = Memory-for-Designs Test, VSM = visual sequential memory, AVLT = Rey's Auditory Verbal Learning Test (1, 5, 6 = trials 1, 5 and 6, respectively; A = List A, B = List B), BVRT = Benton's Visual Retention Test (E = errors, C = correct). ** Postoperative MQ scores for the 2 cases (D.M., M.K.) reported by Campbell *et al.* (1981) are cited in Table 1 from the report by Zaidel and Sperry (1974) and discussed in an earlier section.

significant postoperative memory loss. In both cases, the right fornix had also been sectioned. Van Wagenen and Herren (1940) reported 10 cases in which the corpus callosum was either partially or completely sectioned in order to relieve epilepsy. None of these cases involved postoperative memory deficits, although in 4 of them the left column of the fornix had been sectioned.

Animal studies

The few animal studies that have examined memory following callosal surgery support the view that this structure is not involved in primate memory function. In one study, Rhesus monkeys were tested on an object recognition task following a 1 cm slit in the corpus callosum with transection of the underlying fornix, and compared with a control group in which the fornix had been spared (Gaffan, 1974). The fornix-lesioned group performed significantly worse than controls in both immediate and delayed recognition. Carr (1982) tested 2 baboons who had been trained preoperatively on tasks similar to Gaffan's (1974) recognition task. One baboon with a cut through the genu of the corpus callosum showed no deficit in performing the prelearned task or in learning a new task. The other baboon, who additionally had the fornix transected bilaterally, showed poor recognition memory and failed to perform the previously learned task. These results suggest that the corpus callosum is not involved in memory function and support other work implicating paracallosal limbic structures such as the fornix, mamillary bodies, hippocampus and amygdala (*see* Gaffan, 1983; Zola-Morgan, 1984).

CONCLUSIONS

This review has found no strong evidence for a contribution of surgical lesions of the corpus callosum to recent memory deficits. In the 15 cases that displayed recent memory impairment, many had complicating factors which may have contributed independently to memory impairment, while in the remaining cases there were additional extracallosal lesions to the fornix or hippocampal commissure. In 17 other cases that showed no significant memory impairment following callosal section, there was at most only minimal extracallosal damage.

Although the cases reviewed indicate that memory loss following callosal surgery may be due to damage to the fornix or hippocampus, studies that have directly assessed the issue in humans (*see* Table 4) provide only equivocal evidence. For example, those reporting no memory impairment provide no psychometric data (Dott, 1938; Van Wagenen and Herren, 1940; Cairns and Mosberg, 1951; Garcia-Bengochea *et al.*, 1954; Woolsey and Nelson, 1975). Three studies have reported memory impairment, but one used no psychometric measurement (Hassler and Riechert, 1957) and of two reporting significant IQ-MQ differences (Sweet *et al.*, 1959; Heilman and Sypert, 1977) only one (Sweet *et al.*, 1959) was based on measurement taken 1 yr postoperatively.

TABLE 4 STUDIES IN WHICH FORNIX LESIONS WERE EXAMINED

Case	Lesion	Age at operation (yrs)	Clinical condition	Postop. period (yrs)	Psychometric assessment	Memory function
Dott (1938)						
1 (M)	Bilat. anterior columns of fornix	24	Intraventricular cyst	2	No	No memory deficit noted
Van Wagenen and Herren (1940)						
2 (M)	Division of complete CC, LF	37	Ep.	1	Yes; but no details	Normal
3 (F)	Complete section of CC, LF	28	Ep	0	Yes, but no details	Normal
9 (M)	Complete section of CC, LF	25	Ep.	0	Yes, but no details	?
10 (M)	Complete section of CC, LF	14	Ep.	0	Yes, but no details	?
Cairns and Mosberg (1951)						
7 (M)	Incision ant. forniceal columns, some R frontal lobe removal	40	III vent. cyst	2	No	Memory good
García Bengochea *et al.* (1954)						
12 subjects	Bilat. section of fornix, R trans-frontal approach	17–42	Ep	?	No	Memory not specifically tested
Hassler and Riechert (1957)						
1 (F)	R then L fornicotomy	30	Astrocytoma	0	No	Retrograde amnesia, poor time orientation after LF section
Sweet *et al* (1959)						
1 (F)	Bilat section of ant columns of fornix	36	III vent. cyst	1	Yes IQ = 103	MQ = 90 Defective recall of nonsense syllables— rapid forgetting of current events
Woolsey and Nelson (1975)						
1 (M)	Tumour of posterior columns of fornix	53	—	—	No	No apparent deficit
Heilman and Sypert (1977)						
1 (F)	Neoplasm in HC destroying post fornix bilat.	41	—	0	Yes IQ = 108	MQ = 72. Poor delayed recall of prose, poor face recognition

F = female, M = male, CC = corpus callosum, HC = hippocampal commissure, LF = left fornix, Ep. = epilepsy, MQ = memory quotient, IQ = intelligence quotient.

The assessment of recent memory following surgical section of the corpus callosum must involve psychometric tests that are appropriately discriminating. Only one of the studies reported (Petrucci *et al.*, 1987) has done so and as a result this review has given most weight to the more frequently reported MQ measure and its relationship to IQ. The difficulty, however, is that MQ is relatively insensitive to specific disorders of recent memory (Lezak, 1983) and only two subtests (memory for prose stories and associate learning) can be seriously considered (Walsh, 1978). Sensitive measures of immediate and recent verbal memory may be obtained using the Rey Auditory-Verbal Learning Test (Taylor, 1959) and of visual memory either by the Benton Visual Retention Test (Benton, 1974) or the Complex Figure Test (*see* Lezak, 1983).

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DIAGNOSIS OF UNILATERAL TELENCEPHALIC HEARING DISORDERS

EVALUATION OF A SIMPLE PSYCHOACOUSTIC PATTERN DISCRIMINATION TEST

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SUMMARY

A new psychoacoustic pattern discrimination test (PPDT) has been validated for the diagnosis of telencephalic hearing disorders. In this test, regular sequences of noise bursts or click trains are presented dichotically, and randomly occurring monaural changes in intensity or click pattern have to be discriminated. The PPDT was administered to 48 control subjects and to 62 patients with circumscribed cerebrovascular lesions. Involvement of telencephalic auditory structures (TAS) was assessed from CT scans.

Abnormality in the PPDT was highly correlated with the incidence of a TAS lesion. The most prominent abnormality consisted of an increased error rate (missed discriminations) on the ear contralateral to the TAS lesion, comparable to the ear effect described for former dichotic tests. In normals, no ear dominance, which might have confounded the interpretation of lesion effects in patients, was observed for our test material. Also, the influence of peripheral hearing loss on test results was small.

Criteria for the clinical evaluation of the PPDT were developed and yielded a good sensitivity (76.1%) when related to the CT scan data. Abnormality in the PPDT was also confirmed by reduced auditory evoked dipole source potentials in the lesioned hemisphere. Disturbances in auditory language comprehension in aphasic patients were not significantly related to a positive PPDT result, but a questionnaire about hearing difficulties revealed a close association of PPDT abnormality and auditory perceptual disturbances. These occurred only in difficult hearing environments, for example, the cocktail party situation. It must be concluded that unilateral TAS lesions lead to auditory perceptual impairment and communication problems, which should be given adequate attention during neuropsychological rehabilitation.

INTRODUCTION

Clinically apparent auditory deficits such as 'cortical deafness', 'pure word deafness' or 'auditory agnosia' occur predominantly after bilateral lesions of the auditory cortex and are therefore quite rare (Lhermitte *et al.*, 1971; Goldstein, 1974; Auerbach *et al.*, 1982). These severe clinical symptoms have been described

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only in a few cases after unilateral lesions to telencephalic auditory structures (Liepmann, 1898; Schuster and Taterka, 1926; Spreen *et al.*, 1965). Usually, effects of unilateral lesions on auditory perception appear to be small and not clinically relevant because information presented to either ear can apparently be processed in both hemispheres independently. This idea seems to be supported by the lack of clinically evident symptoms of patients having unilateral lesions of the auditory cortex and by their normal performance in pure tone and monaural speech audiometry (Korsan-Bengtsen, 1973). Also, earlier animal experiments indicated impaired auditory pattern discrimination only after bilateral cortical lesions (Diamond and Neff, 1957), whereas auditory target detection was unimpaired after unilateral lesions (Neff *et al.*, 1975). In contrast, animal experiments using more complex psychoacoustic tasks have revealed impaired auditory discrimination after unilateral ablation of the auditory cortex (Cranford *et al.*, 1971; Jenkins and Masterton, 1982).

Cranford *et al.* (1982) also pointed out that after unilateral lesions in patients, more refined discrimination tasks can unmask an auditory perceptual deficit in contralateral hemispace. These authors could not confirm contralaterally increased thresholds for mere detection of short stimuli reported in the Russian literature (Karasseva, 1972). Summarizing the literature on patients with unilateral lesions to telencephalic auditory structures, experiments using both nonspeech (Cranford *et al.*, 1982; Efron *et al.*, 1983, 1985) and speech material (Bocca *et al.*, 1955; Kimura, 1961; Berlin *et al.*, 1972; Michel *et al.*, 1982) have mostly shown poorer performance for contralaterally presented stimuli (for an extensive review, *see* Pinheiro and Musiek, 1985*a*). However, also a bilateral decrease in performance has been found in a nonspeech frequency pattern task (Musiek and Pinheiro, 1987). In dichotic speech tests even a suppression of the ipsilaterally presented material has been observed (Sparks *et al.*, 1970; Damasio and Damasio, 1979).

Clinical testing of central auditory dysfunction is predominantly based on dichotic speech tests using stimulus material of varying difficulty, like digits, words or sentences (Jerger and Jerger, 1975; Musiek and Pinheiro, 1985). Nonspeech tests examining, for example, temporal order (Swisher and Hirsh, 1972), auditory memory and discrimination of tonal sequences (Milner, 1962; Pinheiro, 1976; Pinheiro and Musiek, 1985*b*) or brief tone discrimination thresholds (Cranford *et al.*, 1982) have not yet become a clinical audiological standard, partly because of task difficulty or limited sensitivity and partly due to lack of validation in larger clinical populations. Also, the small number of available tests warranted a further search for a practical central auditory test.

Our aim, therefore, was to develop a simple and reliable clinical test which could detect unilateral telencephalic hearing disorders in patients. The test should not employ speech material to prevent the confounding of auditory and speech perceptual deficits and to allow testing of aphasic patients as well. This study presents a detailed description and validation of a new psychoacoustic pattern discrimination test (PPDT) in a large group of patients with circumscribed cerebrovascular lesions. Also, PPDT test results will be related to an evaluation of auditory perceptual problems in these patients. Preliminary results using this test and comparing it to auditory evoked dipole source potentials in a small patient group have been published previously (Scherg and von Cramon, 1986*a*).

METHODS

Subjects

A group of 62 patients suffering from unilateral cerebrovascular lesions was tested for central hearing disorders. The time interval from the lesion was more than 3 months in all cases. In the majority of patients (50) an ischaemic infarct had occurred which according to CT scan and clinical evaluation affected one or more branches of the middle cerebral artery (42), the anterior choroidal artery (4) or the posterior cerebral artery (8). The other patients had had haemorrhages within areas supplied by the middle cerebral artery (8) or within the basal ganglia (2) or extending from the thalamus into subcortical white matter (2). The lesion affected the left hemisphere in 47 and the right in 15 patients. Of the 47 patients with left hemisphere lesions, 34 had aphasic disturbances, 29 with and 5 without impaired auditory language comprehension according to the Aachen Aphasia Test (Huber *et al.*, 1983). Patients were from 21 to 70 yrs of age with the majority between 35 and 65; mean age was 48.5 yrs.

The control group consisted of 48 subjects and was closely matched in age (mean age 48, range 20-73 yrs) to the patient group. Control subjects were paid volunteers without a history of neurological disease, but subjects with peripheral hearing loss were not excluded as moderate hearing loss due to noise exposure, age, hereditary and toxic causes is quite common in comparable normal populations. The mean hearing loss (audiometric thresholds averaged over frequencies 0.5, 1, 2 and 4 kHz and for both ears) ranged from 5 to 51 dB (median 13) in the patient group and from 1 to 51 dB (median 10) in the controls. Mean differences between ears (left-right mean threshold) ranged from −15 to 12 dB in the patients and from −9 to 22 dB in the controls. Informed consent was obtained from all subjects.

Psychoacoustic pattern discrimination test (PPDT)

The PPDT consisted of 2 subtests devised to monitor the discrimination of changes in intensity (DI) and changes in temporal structure (DT), respectively, within a periodically presented stream of acoustic stimuli. A simple oddball paradigm was used in which randomly occurring target stimuli replaced the regular standard stimuli. Subjects had to press a button whenever they could discriminate a target within the stimulus stream irrespective of the side of presentation. Stimuli were 200 ms noise bursts in the DI and click trains in the DT subtests, regularly presented every 600 ms (fig. 1A). Signals were delivered dichotically, i.e., in subtest DI incoherent noise bursts were presented to the right and left ears to minimize binaural interaction as a potential cue for discrimination. Also for this reason, in subtest DT click trains (interclick interval 36 ms, click duration 0.1 ms) were interlaced between ears such that a train of 6 clicks was presented to one (leading) ear and a train of 5 to the other ear (fig. 1C). Thus the time interval between a click in one ear to the next click in the other ear was 18 ms, the duration of the standard stimulus train being 180 ms in the leading ear The leading side was alternated after each stimulus presentation. Over the 4 test runs the leading side was counterbalanced (beginning side scheme: A,B,B,A)

Monaural changes of the standard stimuli served as targets. They occurred at every 6-10th stimulus (intertarget interval 3.6-6 s) and were randomized between ears with a maximum of 2 successive targets on the same side. In each run 10 targets, 5 to each side, were presented. Targets were constructed by digitally amplifying the noise burst at the target ear by 10, 6 or 4 dB (test levels 1-3, fig. 1B). Targets in the DT subtest were formed by shortening the click train in the nonleading

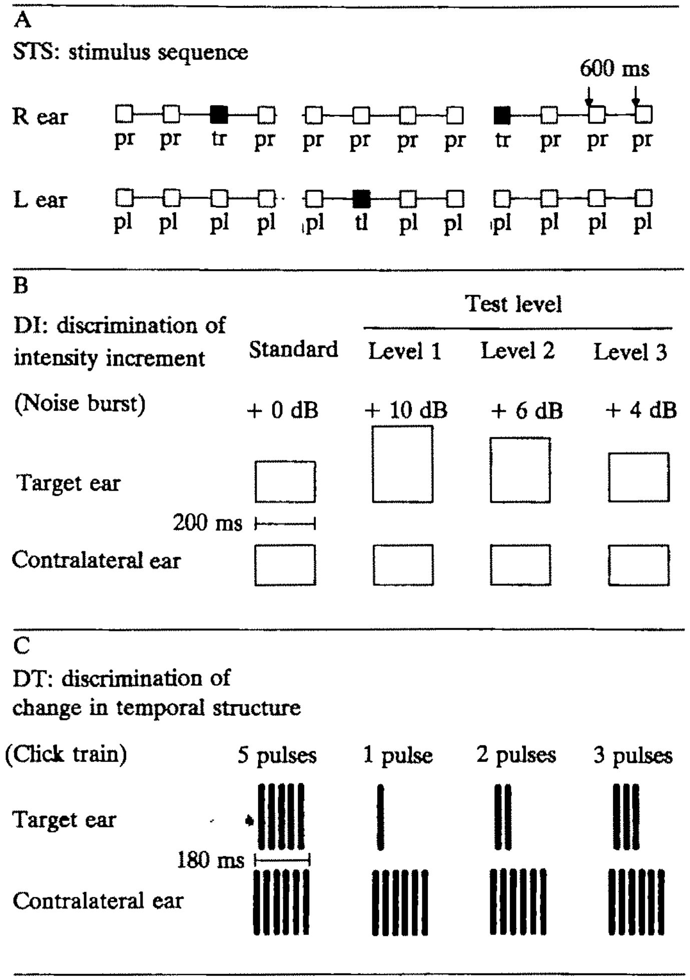

FIG 1. PPDT stimulus paradigm A, a periodic stimulus stream (ISI 600 ms) is synchronously delivered to right (pr) and left (pl) ears. Monaural targets (tr, tl) replace a periodic stimulus at randomized intervals. B, in subtest DI, incoherent digital noise bursts of 200 ms duration are used as periodic standards. An intensity increment of 10, 6 or 4 dB forms a target with difficulty levels 1-3, respectively. C, in subtest DT, the periodic standard stimulus consists of interlaced trains of 6 clicks to one ear and 5 to the other. Targets are formed by presenting only 1, 2 or 3 pulses (corresponding to levels 1-3) instead of 5 to the nonleading ear.

ear (fig. 1C). Instead of having 5 clicks, the train was terminated after 1, 2 or 3 clicks (test levels 1-3). Targets were easy to discriminate at level 1 and could just be heard at level 3 by normal listeners.

Procedures

A pure tone audiogram was obtained in all subjects before applying the PPDT. Patients often stated that they did not have any hearing complaints. To establish whether they had an auditory perceptual problem which they possibly did not experience as a hearing problem, a systematic set of questions regarding possible auditory perceptual problems in certain everyday situations was introduced after the first phase of PPDT testing in patients. This questionnaire was given to 45 patients without severe aphasic or cognitive impairments. Patients were asked, for example, how well they could follow conversations in noisy environments or in situations with several simultaneous speakers, or how they perceived interfering acoustic events.

Speech audiometric tests and the most common German dichotic test (speech material of 4 syllables, Feldmann, 1965) could not be administered to many subjects because of aphasic or memory problems. Auditory evoked potentials (AEPs), i.e., middle and late latency dipole source potentials (for methods, *see* Scherg and von Cramon, 1986*a*, *b*), served as an independent control of telencephalic auditory function in 32 patients, but were not recorded in all subjects because of the excessive diagnostic time needed.

Testing was done in a sound-attenuated room with the patient sitting in a comfortable armchair. As for audiometry, in the PPDT, subjects were instructed to press a button when they could discriminate a change in the regular acoustic stimulus pattern. Subjects were told that they should perform the test as accurately as possible and that speed of reaction was not important. The instruction to react only to targets was rapidly learned, even by aphasic patients, when the target was easy to discriminate. Testing therefore began with a training run at level 1 changing intensity (DI). After at least 5 subsequent correct discriminations at this level, the run was terminated and a full run at level 2 was given. If the discrimination rate was above 50%, difficulty was increased to level 3 and 4 runs were completed at this test level. Otherwise, or when the discrimination rate at level 3 fell below 40%, testing was completed to 4 runs at level 2. The same test sequence was subsequently applied for changes in temporal structure (DT). Including pauses, this procedure lasted only 15–20 min and thus the PPDT could usually be performed, along with the audiometry, during a single session. In 6 patients, studied in the initial period of test development, a total of only 6 runs (3 per subtest) was collected.

For the PPDT, acoustic signals were generated by computer using 2 digital to analog converters (DACs). Noise bursts were generated by routing 2 independent series of pseudorandom numbers to the 2 DACs (numbers equally distributed over the DAC range, digitization rate 10 kHz). After low-pass filtering (4 kHz, −6 dB down, 24 dB/oct slope, Bessel type) stimuli were presented through lightweight earphones (Sony MDR-M55) for subject comfort. Stimulus level was 63 dB SPL for the noise bursts and 85 dB peSPL for the click trains as measured with a precision sound level meter (Brüel and Kjaer 2233). These stimulus levels corresponded to an approximate sensation level of 60 dB SL for normal hearing adults. Stimulus level was raised by 10 dB at one or both ears if the audiogram had shown monaural or binaural peripheral hearing loss of at least 20 dB. Reaction time was measured via a digital input. Correct target detection was assumed for reaction times ranging from 200–1800 ms after the relevant change in the signal (an extra delay of 54, 96, 132 ms was taken into account for DT levels 1–3, respectively). Error scores included misses (no response) and false responses (button press outside permissible range), which rarely occurred (*see* Results).

PPDT data evaluation

The following raw data parameters were derived from the error scores at each ear (Blaettner, 1989). Absolute error (AE) percentage scores were calculated from the total number of errors at both ears divided by the total number of targets (40) in the 4 test runs, for each subtest separately. Difference error (DE) percentage scores were derived from the number of left ear errors minus right ear errors divided by the number of targets to one ear (20) in the 4 test runs. Thus a DE of +100 would indicate a 100% failure in discrimination of left ear targets, whereas negative values would indicate a higher number of right ear errors.

The Wilcoxon matched-pairs signed rank test was used to assess differences of the AE and DE scores in both subtests. Because performance was not significantly different for the complete patient group nor in any of the subgroups, combined error scores were computed from the mean values in both subtests. Further parameters were the 'sign of DE', indicating the side having the higher mean error score, and 'level' (set to 1 if level 3 passed, set to 0 if failed in either subtest). Group differences were evaluated statistically using the Mann-Whitney U test and a linear discriminant analysis was performed to test the ability of the PPDT to classify cases of central hearing disorders (Blaettner, 1989).

Validation of the PPDT was performed by one of us (Blaettner, 1989) using the same control but different patient groups defined by vascularization criteria. Processing and presentation of raw data, statistical methodology, evaluation of diagnostic criteria and of a classification rule, including reclassification, were undertaken as in Blaettner (1989).

CT scan evaluation

CT scans were available for all patients and were evaluated independently by one of us (D.v.C.) for damage to telencephalic auditory structures (TAS), with separate estimates for 5 areas: (1) medial geniculate body and proximal auditory radiation (PAR); (2) distal auditory radiation (DAR); (3) primary auditory cortex (AI/AII); (4) auditory association area I (AAI); (5) auditory association area II (AAII). Three probabilistic classes of judgements were defined: no, questionable and most likely involvement of the respective structure. Because in many patients several areas were involved and hence the number of cases having an isolated involvement of only one structure were too small for statistical evaluation, a posteriori this CT classification was collapsed into three groups as follows (not distinguishing between questionable and most likely judgements): (1) no lesion in TAS: none of the 5 areas involved (16 subjects); (2) lesions of the acoustic radiation (AR) only without cortical involvement (PAR and/or DAR affected, 15 subjects); (3) lesions involving at least one auditory cortical (AC) area (AI/AII, AAI of AAII), irrespective of the extent and of possible additional involvement of subcortical white matter (31 subjects).

Finally, for the presentation of the raw data, 4 groups were distinguished: control subjects (48), patients having no TAS lesion according to the CT scan (16), patients having a right hemisphere AR or AC lesion (12) and those having a left AR or AC lesion (34).

RESULTS

PPDT raw data

First, an analysis of the type of errors and of a potential trend over the 4 test runs was undertaken. Errors consisted almost exclusively of missed targets. In the control group the mean AE score over subtests and runs was 7.5%, comprising 7.06% misses and 0.44% false alarms. For the patient groups, mean AE was 28.9%, comprising 27.1% misses and 1.8% false alarms. Thus the relative proportion of false alarms in AE scores was about the same in the control (5.9%) and patient (6.2%) groups. False alarms would have increased by only 0.3% and 1.5% (relative proportions 9.1% and 11%) for both groups, respectively, if responses later than 1200 ms after the relevant change in the stimulus pattern had been counted as false alarms. A shorter reaction time limit, however, would have increased the proportion of false alarms dramatically, for example, to 47% in both groups for a 600 ms limit. In all, only 1 control subject and 4 patients had error scores with a proportion of more than 20% false alarms for the reaction time limit of 1800 ms. This limit was finally retained for all analyses, because the test instruction did not emphasize speed of reaction and because the increase in error scores, caused by more false alarms, was minimal for the earlier cut-off at 1200 ms. Also we did not want to confound errors due to generally slowed responsive behaviour with auditory discriminative disturbances.

No significant trend was found across the 4 test runs which might have indicated a possibility for strategies to improve during the course of the test (Friedman's test for matched groups, i.e., runs: $\chi^2 = 6.0$, df = 3, $P > 0.1$ for controls; $\chi^2 = 4.9$, df = 3, $P > 0.1$ for patients). For the control group, mean AE scores were 9.6% in the first run and 7.2% in the last run; for patients, mean AE scores were 26.5% in the first and 29.9% in the last run. Because of a missing trend and consistent differences between controls and patients over runs, for the following analyses error scores were computed from the means over all runs as described in the Methods section.

TABLE 1. COMPARISON OF PATIENT AGAINST CONTROL GROUPS FOR PPDT PARAMETERS AE AND DE*

Group Variable	*Lesion in left TAS* ($n = 34$)	*Lesion in right TAS* ($n = 12$)	*No lesion in TAS* ($n = 16$)
AE	$P < 0.001$	$P < 0.001$	n.s.
	Z = −5.92	Z = −5.28	Z = −1.71
DE	$P < 0.001$	$P < 0.001$	n.s.
	Z = −5.49	Z = −5.10	Z = −0.98

* Mann-Whitney U and Wilcoxon rank sum test.
AE = absolute error score, DE = difference error score (L-R).

Histograms of absolute and difference error scores (AE, DE) are depicted in fig. 2 for the different control and patient groups. On test level 3, all control subjects had low absolute and difference error scores, with a maximal range of 25% for AE and ±20% for DE. Similarly, of the 16 patients without a TAS lesion, only 4 fell outside this range while all passed the test at level 3. In contrast, the majority of patients with suspected TAS lesions had increased error scores. Twelve of these patients failed the test criteria at level 3.

In patients with TAS lesions, the most conspicuous finding was the clear lateralization of the difference error score towards the ear contralateral to the lesioned hemisphere (DE in fig. 2), positive values of DE indicating a higher rate of errors for left ear targets, negative values for right ear targets. Differences between the two patient groups with right or left hemisphere TAS lesions and the control group were highly significant (Table 1, $P < 0.001$ for AE and DE, Mann-Whitney U test), whereas the patient group without TAS lesions did not deviate from normal. Only a few patients scored 100% correct in one ear, while having a large error score for the ear contralateral to the lesioned hemisphere. Mostly, AE was increased above the amount accounted for by DE because some errors also occurred on the ipsilateral ear. However, in all patients with abnormal AE (for criteria, *see* below) the sign of DE indicated a higher error score for stimuli delivered contralaterally to the lesion. Patients with right TAS lesions exhibited

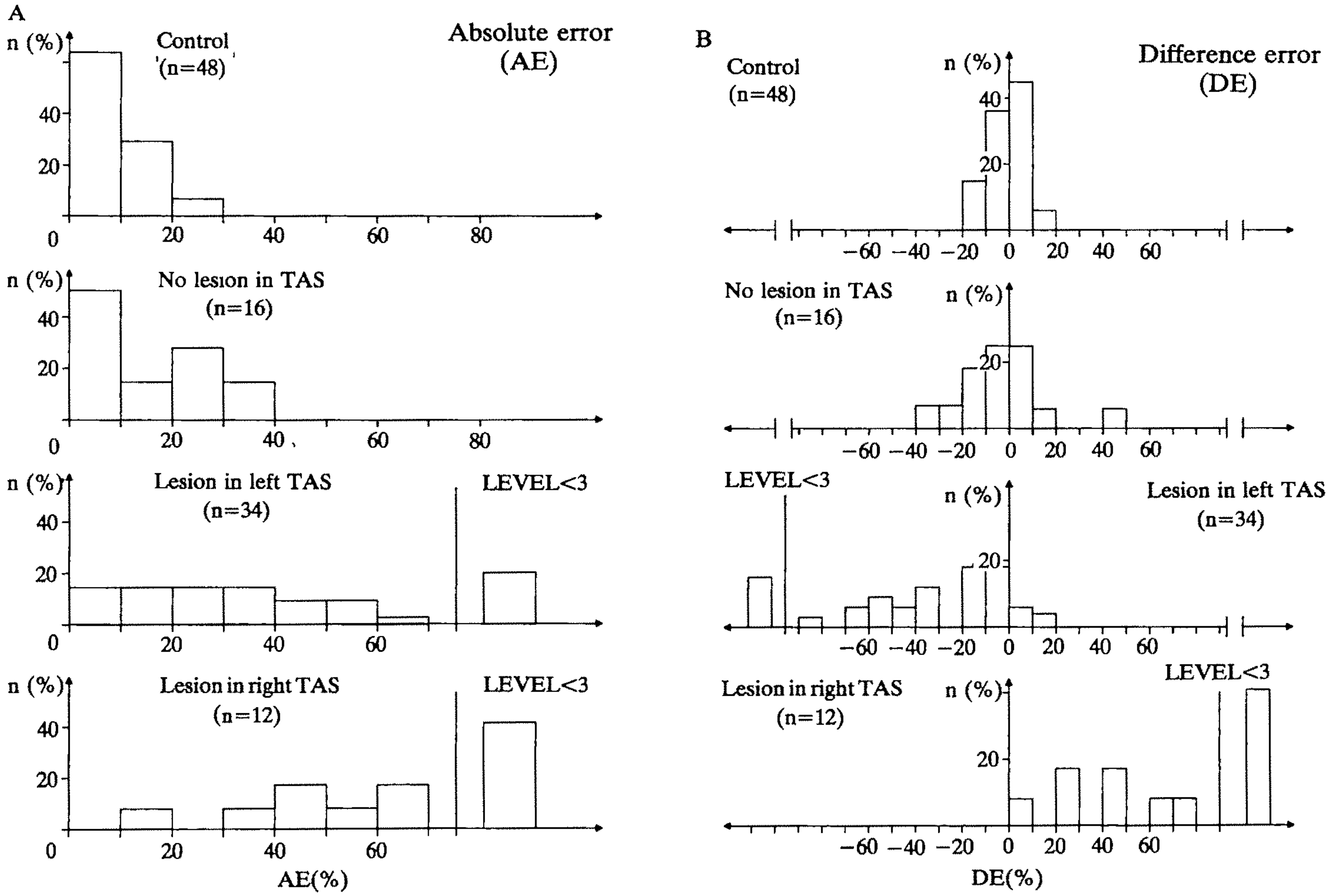

FIG. 2. Percentage histograms of main PPDT variables for the control and patient groups According to CT scans, patients were grouped into subjects without lesions of telencephalic auditory structures (TAS, 16) and subjects with left (34) and right (12) TAS lesions. PPDT variables were absolute error percentage score (A, AE, total no. of errors) and difference error percentage score (B, DE, left-right ear errors). Columns level < 3 indicate percentage of subjects failing level 3 Note the clear lateralization of DE scores to the contralateral ear. Note also that there was no ear dominance in the control group (mean DE −1.2±6.5%).

TABLE 2. RECLASSIFICATION BY LINEAR DISCRIMINANT ANALYSIS

	Predicted group membership			
Actual group	*No TAS lesion (normal)*	*Lesion in left TAS*	*Lesion in right TAS*	*Total*
No TAS lesion	12	3	1	16
Lesion in left TAS	11	23	0	34
Lesion in right TAS	1	0	11	12
Controls classification	47	1	0	48

larger AE scores than patients with left TAS lesions (Mann-Whitney U test, $Z = -2.28$, $P < 0.05$), while the size of the laterality effect, that is, the magnitude of the DE scores, was not significantly different between both groups (Mann-Whitney U test, $Z = -0.5$, $P > 0.62$).

Evaluation of diagnostic criteria

Discriminant analyses were performed to explore the diagnostic value of using a combination of the described parameters in classifying individual cases (Blaettner, 1989). When contrasting the no TAS lesion group against the right and left TAS lesion groups (Table 2), a good separation between these three patient groups could be seen (74.2% correctly reclassified). Only 12 of the 46 TAS lesion cases were reclassified as normal (false negatives) and 4 patients of the no lesion group were reclassified as abnormal (false positives). This analysis, based only on the patient groups, classified all but 1 control subject as normal (overall correct reclassification 84.5%). When controls and the patient group without TAS lesions were combined in the discriminant analysis, classification results were identical with those shown in Table 2 for patients only.

The main result of these analyses was that the subtest variables did not improve discrimination above that obtained by the global variables AE, DE, 'level' and 'sign of DE'. The results in Table 2 are based on these 4 variables with a priori probabilities of 0.4 for the no TAS lesion group and 0.3 for both TAS groups.

The global variables 'level', AE and DE and 'sign of DE' were therefore retained to define a classification rule (Blaettner, 1989) for diagnostic application of the PPDT, as illustrated in fig. 3. One clear cut-off criterion could immediately be derived from the observation that all controls and subjects without TAS lesions could perform the test at level 3, while 12 patients with TAS lesions had failed. Also, letting cut-off to 30% for the absolute error score and to ±30% for the difference error score appeared to be a safe margin above the upper range of the normal group, making a false positive judgement less likely. Reclassification results based on this diagnostic rule are shown in Tables 3 and 4. In any case, a highly

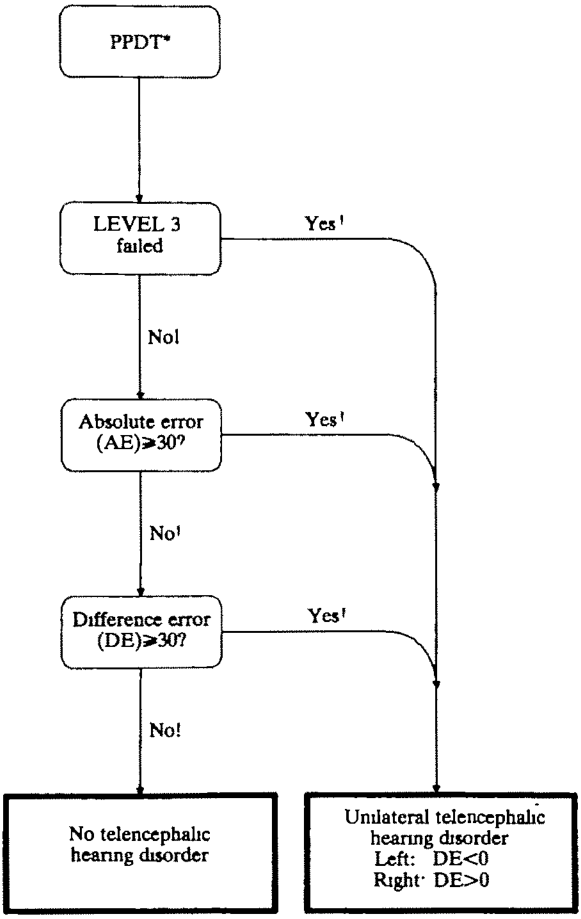
PPDT*
LEVEL 3 failed
Yes¹
No!
Absolute error (AE)≥30?
Yes¹
No¹
Difference error (DE)≥30?
Yes¹
No!
No telencephalic hearing disorder
Unilateral telencephalic hearing disorder
Left: DE<0
Right: DE>0

FIG. 3. Flow diagram of decision rule for PPDT evaluation. Decision on abnormality is based on the following hierarchic steps: (1) failure at level 3; (2) absolute error score exceeds 30%; (3) magnitude of difference error score exceeds 30%. If any of these 3 conditions is met, the test is abnormal. The sign of DE points to the affected hemisphere * These test criteria for the diagnosis of a unilateral telencephalic hearing disorder hold only for cases of unilateral cerebrovascular disease.

significant effect of TAS lesion on the PPDT result was seen when controls and subjects without TAS lesions were contrasted separately ($\chi^2 = 55$ and 11.2, respectively, df = 1, $P < 0.001$) or in combination ($\chi^2 = 54$, df = 1, $P < 0.001$) against all patients with TAS lesions (Table 3). The overall hit rate (% of correctly reclassified cases) of the PPDT was 86.4% using the CT evaluation as independent reference criterion. The sensitivity (% of correctly detected abnormal cases) was 76.1% and specificity (% of correctly reclassified normal cases) was 93.8% when the control and no TAS lesion groups were combined (100% and 75%, respectively, for separate groups).

Table 3 shows that all control subjects were reclassified as normal. The 4 false positive cases belonged to the group of 16 patients without TAS lesions according

TABLE 3 RELATION OF PPDT RESULT TO INCIDENCE OF LESIONS OF TELENCEPHALIC AUDITORY STRUCTURES (TAS) NO OF CASES

		Patients *Lesion in TAS*	
PPDT	*Controls*	*No*	*Yes*
Normal	48	12	11
Abnormal	0	4	35

TABLE 4. RELATION OF PPDT RESULT TO SITE OF LESION NO OF CASES IN PATIENT GROUP

PPDT	*No lesion in TAS* $n = 16$	*TAS lesion (AR group)* $n = 15$	*TAS lesion (AC group)* $n = 31$
Normal	12	7	4
Abnormal	4	8	27

AR group: lesion presumed only to affect acoustic radiation; AC group. lesion comprised at least one auditory cortical area.

to CT criteria. A normal, false negative, classification (11 cases) in the TAS lesion groups occurred predominantly in cases when only the acoustic radiation seemed to be involved (Table 4: 7 cases versus 4 with auditory cortical involvement). In 5 of these 7 cases with suspected AR lesions and normal PPDT the CT had been judged to show a questionable lesion only. Altogether, 8 of the 15 cases with damage to the acoustic radiation only were abnormal in the PPDT (CT abnormality judgement most likely in 5 subjects). Of the 31 patients with auditory cortical involvement, 27 were classified abnormal and only 4 normal. One subject amongst these 4 false negative cases showed a lesion only in AAII.

Relation between PPDT performance and region of infarction

An attempt was made to relate PPDT results to the region of cerebral blood supply affected by the lesion, as evaluated from CT scan and clinical data. When the patients with ischaemic infarctions were categorized according to which branch of the middle (MCA) or of the posterior (PCA) cerebral artery was predominantly involved (MCA: subtotal, posterior, central, anterior and lateral striate artery; PCA: mesencephalic artery branches), 100% abnormality was observed after subtotal MCA infarctions or infarctions of the anterior choroidal artery (ACHA). Abnormality was 74%, when posterior and/or central MCA branches were affected (fig. 4). In contrast, patients with infarctions of the anterior MCA branches or of PCA performed normally in the PPDT. However, the small sample sizes prohibited a statistical evaluation for each region of infarction.

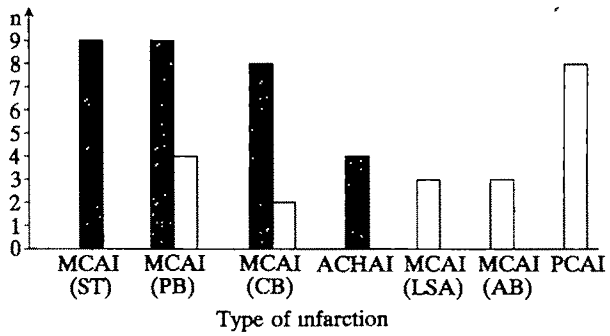

FIG 4 Relation of PPDT result (normal, open areas, abnormal, hatched areas) to main region of infarction. All subjects with subtotal infarction in middle cerebral artery territory (MCAI, ST) and infarction of the anterior choroidal artery territory (ACHAI) had abnormal PPDT scores. Most infarctions in the distribution of the posterior (PB) and central (CB) branches of MCAI also resulted in abnormality, whereas the PPDT was normal for infarction in the distribution of the lateral striate artery (LSA) and anterior branches (AB) of the MCAI and the posterior cerebral artery (PCAI). In these groups a few patients had additional lesions in the territories of other branches or arteries (MCAI (ST): 1 ACHAI; MCAI (PB): 2 CB, 2 LSA, 1 CB+LSA; MCAI (CB): 5 AB, 3 LSA, 1 AB+LSA; ACHAI: 1 MCAI (LSA), 1 PCAI; MCAI (LSA): 1 AB).

TABLE 5 RELATION OF PPDT RESULT TO EVALUATION FOR CENTRAL HEARING DISORDER AND AUDITORY EVOKED POTENTIALS (AEPs)

	Evaluation of central hearing disorder ($n = 45$)		*AEP* ($n = 32$)	
PPDT	*Normal*	*Abnormal*	*Normal*	*Abnormal*
Normal	18	3	6	6
Abnormal	5	19	0	20

Correlation with evaluation for central hearing disorder

Careful questioning of the patients on potential auditory or speech perceptual problems in complex everyday hearing situations revealed a surprisingly high incidence of reported problems (Blaettner, 1989). It was possible to administer such a hearing questionnaire to 45 patients, usually before audiometry and PPDT were undertaken; 49% of these patients reported perceptual problems, most commonly in situations with several simultaneous speakers. Some reported sounds to be duller or blunted on the ear contralateral to the lesion, although there was no equivalent loss in tone audiometry thresholds. There was a highly significant positive correlation ($\chi^2 = 16.4$, df $= 1$, $P < 0.001$) between PPDT results and the evaluation of central hearing disorder. Table 5 shows that 19 of 24 patients (79%) with an abnormal PPDT performance reported difficulties in auditory perception, whereas this was negative in 18 of 21 cases (86%) with normal PPDT.

Correlation with auditory evoked dipole source potentials

As for the assessment of central hearing, a high correlation between PPDT and middle and late latency AEP results was similarly found for the 32 patients who had undergone both examinations (Table 5, $\chi^2 = 9.2$, df = 1, $P < 0.001$). Abnormal PPDT results were confirmed in all 20 cases by abnormalities in the AEP, i.e., by hemisphere differences of dipole source potentials, mainly amplitude reductions of the dipole moment in the affected temporal lobe (for criteria, *see* Scherg and von Cramon 1986*b*). In contrast, the AEP was also abnormal in 6 of 12 patients with normal PPDT. In 4 of these cases with abnormal AEP, involvement of TAS was confirmed by the CT scan (3 AR, 1 AC). Considering the 4 false positive PPDT cases (with respect to CT criteria) for the 16 subjects in the no TAS lesion group, the functional deficit in 2 of them was confirmed by an AEP abnormality, while the 2 others, who had no AEP recorded, had a positive central hearing anamnesis. Early AEPs, recorded simultaneously with the middle latency AEPs, showed normal transmission in the lower brainstem in all patients.

Correlation with aphasic disturbances

Of the 47 patients with left hemisphere lesions, 34 were aphasic according to the Aachen Aphasia Test (Huber *et al.*, 1983). While the 13 patients without aphasia showed both normal (8) and abnormal (5) PPDT results, the incidence of PPDT abnormality was only slightly, but not significantly larger in the aphasic group (21 abnormal versus 13 normal in the PPDT, $\chi^2 = 1.23$, $P = 0.27$). Also, when comparing the subtest of auditory language comprehension (ALC) with the PPDT result (ALC abnormal: 19 of 29 with abnormal PPDT; ALC normal: 11 of 18 with normal PPDT), there was no significant correlation ($\chi^2 = 2.2$, $P = 0.14$).

DISCUSSION

Our main aim of developing an easy and sensitive central auditory test, reliable also for aphasic subjects and fairly insensitive to peripheral hearing loss, seems to be achieved with the PPDT. First, the PPDT is not a dichotic test in the sense that recognition of two independent stimuli presented simultaneously to both ears is required. In that respect and with regard to complexity of material, it is substantially simpler than the common dichotic speech tests using numbers, words, sentences or melodies (for an extensive review of these tests, *see* Musiek and Pinheiro, 1985). In patients with temporal lobe damage these tests have shown decreased recall mainly for material presented contralaterally to the brain-damaged side (Kimura, 1961; Shankweiler, 1966; Musiek, 1983). But after left-sided lesions, often associated with aphasia, not only clear contralateral (Michel *et al.*, 1982) but also bilateral (Schulhoff and Goodglass, 1969; Musiek, 1983) and even severe ipsilateral deficits (Sparks *et al.*, 1970) in dichotic speech tests have been reported.

Michel *et al.* (1982) have stressed the importance of distinguishing between auditory and speech perceptual disturbances, which is impossible using a dichotic speech test. They showed cases with a left hemisphere lesion without language disorders but unilaterally decreased AEPs, who had clear contralateral deficits up to a complete suppression of the speech information presented to the right ear. The PPDT appears to circumvent these problems because it permitted detection of disturbances at the auditory level independent of the presence of aphasia. Our results also indicate that telencephalic hearing disorders can be present without necessarily entailing aphasic problems. Thus the coincidence of auditory perceptual and aphasic disturbances may merely be a consequence of the cerebrovascular lesion extending both to auditory areas and to relevant speech areas. However, that unilateral cerebral auditory dysfunction plays a role in the severity of aphasia cannot be dismissed or established on the basis of our data.

Because the PPDT had been designed as a suprathreshold test and not as a threshold detection test, symmetric peripheral hearing loss, especially in the high frequencies, had little influence on PPDT test results for normal subjects and did not mask the lesion effect in patients (Blaettner, 1989). Also, the negligible, nonsignificant correlation of the difference error score with threshold differences between ears indicates a high degree of robustness against peripheral factors. This stands in contrast to dichotic speech tests, which are severely influenced by peripheral hearing loss (Speaks *et al.*, 1985). The PPDT seems to share this high independence on cochlear factors only with one other nonspeech test, the frequency pattern test by Pinheiro (Pinheiro, 1976; Musiek and Pinheiro, 1987).

Apart from the small influence of aphasic, memory and peripheral hearing problems, another advantage of the PPDT is that it did not exhibit an ear dominance in normals nor was the size of the laterality effect larger in either the right or left hemisphere lesion groups. This may indicate that the PPDT tests a low level of auditory processing at which hemisphere specialization is not yet effective. In other dichotic tests, including nonspeech tests (Yund and Efron, 1976; Sidtis, 1981; Gregory *et al.*, 1983), ear dominance for spectral or temporal features is important (Divenyi and Efron, 1979) and may be confounded with a lesion effect. In the PPDT, only the most severely abnormal subjects had increased error scores in both ears, for example patients failing level 3. This may suggest that impairment was not restricted to auditory perception in one hemispace in these cases. In all patients however, the laterality effect, as reflected in the difference error score, indicated more impaired performance contralaterally.

The comparison of PPDT and CT scan data showed that involvement of telencephalic auditory structures most probably leads to an abnormal test result. Cerebrovascular lesions in other telencephalic brain areas, even in close vicinity, such as areas supplied by the anterior branches of the middle cerebral artery, did not cause abnormality. Yet the small number of cases in subgroups with a lesion to one specific area only, especially those with lateral striate artery (LSA) and anterior choroidal artery (ACHA) infarctions, did not allow a separate statistical evaluation for each area. Nevertheless, it was evident that both subcortical lesions affecting the acoustic radiation (most likely in the 4 ACHA and in the 1 LSA infarctions) and lesions affecting the auditory cortex (most MCA cases) can result in central auditory dysfunction as indicated by the PPDT results. Because CT scans were not available or not evaluated specifically with regard to TAS lesions, former studies on central auditory dysfunction in patients could not demonstrate convincingly this close connection of auditory telencephalic and perceptual defects. An exception is the study of Cranford *et al.* (1982) on brief tone discrimination limens, also showing clear contralateral discrimination deficits after lesions to relevant auditory areas only. Although the frequency pattern test of Musiek and Pinheiro (1987) exhibited a high sensitivity to cerebral lesions similar to that of the PPDT, a detailed correlation of lesion site and test results was not presented in their paper. Most of their patients also had different aetiologies not allowing precise circumscription of lesion areas.

Contralateral deficits have also been observed by Efron and his collaborators (Efron and Crandall, 1983; Efron *et al.*, 1983, 1985) after temporal lobectomies sparing Heschl's gyri. These authors explained their findings of impaired pitch, spatial and temporal resolution in terms of an affected 'temporal lobe enhancement mechanism', which they suggested may subserve selective attention by each hemisphere for contralateral hemispace, for example in cocktail party situations. We propose that the deficits observed in our patients reflect a disturbance of a similar or the same mechanism and that this mechanism requires the intact collaboration of telencephalic structures ranging from the acoustic radiation up to the cortical association areas AAI and AAII. In our patient group, isolated lesions of the acoustic radiation and/or of areas AI/AII were sufficient to produce abnormality, while in the cases with temporal lobectomies partial damage of AAI and AAII or of subcortical connections to AI/AII seems very probable.

Which features of the PPDT are essential for revealing the central hearing disorder, and what is the nature of the deficit? The clear laterality effects in most patients with unilateral TAS lesions indicate that targets could not be discriminated on the basis of a comparison of the input from both ears within the intact hemisphere. Apparently the dichotic presentation of two regular stimulus streams required an independent analysis of each stream in the contralateral hemisphere, because binaural cues were minimized in the design of the PPDT. It may be concluded that, independently for each stimulus stream or for each hemispace, short term (400–600 ms) storage of and comparison against previous stimuli is necessary for the discrimination of a change in a certain stimulus cue.

Two cues were modified in this study, intensity and temporal structure, and for both cues similar lesion effects occurred when the difficulty level was raised to the level at which discrimination was just possible for normal subjects. For the few subjects responding abnormally only to one cue, a systematic relation to a specific region of infarction within telencephalic auditory structures could not be established. Hence one may conclude that unilateral abnormality in the PPDT reflects basic auditory perceptual deficits in the hemispace contralateral to the lesion, which may become manifest to a different degree within various acoustic categories. For example, contralaterally impaired pitch discrimination for short stimuli has also been observed after unilateral temporal lobe damage (Cranford *et al.*, 1982).

Whether the lesion effects of the PPDT reflect a purely perceptual or an attentional deficit, cannot easily be answered. This problem has been raised by Gregory *et al.* (1983) with respect to ear dominance for pitch. When we asked patients to focus attention on the ear on which they missed many targets, they did not improve nor had they noticed their poorer performance. It may be hypothesized from these observations that the auditory cortex subserves both awareness and discrimination of acoustic stimuli, predominantly in the contralateral hemispace. It is remarkable in this context that our central hearing questionnaire revealed that these patients did not experience a hearing problem but rather discomfort or overload, leading to poorer understanding of speech in social situations demanding high auditory selectivity.

Preliminary results of the PPDT in a patient group suffering from severe closed head trauma have shown high absolute error scores in the first few months after the trauma with a progressive recovery up to normal. This indicates that global attentional deficits after diffuse brain damage may also impair performance in the PPDT. While the value of the test to monitor general auditory attentional problems remains to be shown, application of the PPDT for central hearing diagnosis must be restricted to cases of localized telencephalic brain dysfunction, such as cerebrovascular disease, for which specificity was very high.

The comparison of the PPDT against AEP results provided an interesting insight into the value of auditory evoked potentials in functional diagnosis. The middle and/or late AEPs were abnormal in all cases with abnormal PPDT, but the reverse was not true. Thus the AEPs appeared more sensitive to a lesion of the generating substrate, although function may not yet be sufficiently disturbed to produce abnormal PPDT results. However, this higher sensitivity to structural damage of the AEP can only be obtained if the scalp activity is adequately separated into dipole source activities of each temporal lobe, thereby enabling an optimal interhemispheric comparison (Scherg and von Cramon, 1986*a*, *b*).

A surprising finding was the high association between a positive report in the auditory perceptual questionnaire and PPDT abnormality. Only reports on severe, clinically evident, hearing problems, mostly after bilateral and rarely after unilateral lesions, can be found in the literature (Lhermitte *et al.*, 1971; Mazzucchi *et al.*, 1982). Most problems encountered by our patients did not concern hearing as such but speech perception in cocktail party situations or increased irritation by background music, noise or other interfering acoustic events. Patients apparently did not associate these problems with hearing. Although of different origin and probably not comparable in quality, this reduced capacity to follow or select a speaker in a noisy environment resembles similar disabilities occurring after peripheral sensorineural hearing loss. But whereas after peripheral loss the remaining spectral cues provide only insufficient information to the central mechanism of auditory selectivity, after unilateral TAS lesions the mechanism itself seems to be affected.

For adequate consideration of the communication abilities of patients with neuropsychological deficits, especially aphasia, it therefore seems important to be aware of the potential interference of central auditory dysfunction. The PPDT can be a valuable diagnostic tool, indicating that a patient has a central hearing problem. The PPDT of course does not specify details of the dysfunction, but it can assist by giving awareness of a patient's central hearing problem. Difficult hearing situations can then be avoided.

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PROSTACYCLIN AND NORADRENALINE IN PERIPHERAL NERVE OF CHRONIC EXPERIMENTAL DIABETES IN RATS

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SUMMARY

Noradrenaline levels in the superior cervical ganglion and sciatic nerve were significantly reduced in chronic streptozotocin-induced diabetes in rats. Sciatic nerve sheath in vitro biosynthesis of 6-keto prostaglandin $F_{1\alpha}$ (6KPGF$_{1\alpha}$; the stable metabolite of prostacyclin) was significantly reduced but not in acute experimental diabetes. Nerves with reduced 6KPGF$_{1\alpha}$ had an excessive response to arachidonic acid stimulation. We suggest that the reduced endogenous biosynthesis of prostacyclin is due to reduced substrate availability, possibly due to the reduced noradrenaline. The implications of these findings on the pathogenesis of diabetic neuropathy are discussed. Neuropathy was found to involve all fibre populations studied (motor, sensory and sympathetic) and progressed with duration of diabetes.

INTRODUCTION

Microvascular abnormalities are consistently present in human diabetic neuropathy and endoneurial hypoxia is present (Newrick *et al.*, 1986). Nerve blood flow is reduced and endoneurial hypoxia is present in chronic streptozotocin-induced diabetes in rats (Tuck *et al.*, 1984). These changes, which occur by 4 months of diabetes, suggest that the microvascular alterations are important in the pathogenesis of diabetic neuropathy. Further support for the importance of endoneurial hypoxia include the following. Oxygen supplementation will prevent some of the electrophysiological and biochemical abnormalities in peripheral nerve in experimental diabetes (Low *et al.*, 1984; Yao and Low, 1986) Hyperbaric oxygenation will reverse some of the electrophysiological abnormalities (Low *et al.*, 1988) and hypoxia alone will reproduce some of the biochemical and electrophysiological abnormalities of experimental diabetic neuropathy (Low *et al.*, 1986). While pathological alterations in diabetic nerve are minor, the superimposition of ischaemia will result in more extensive fibre degeneration than in controls (Nukada, 1986).

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Little information is available on neurovascular vasoreactivity in normal and diabetic nerves. Noradrenaline (NA) is the major neurotransmitter in the mammalian peripheral nerve sheath (Appenzeller *et al.*, 1984; Rechthand *et al.*, 1986) and the ratio of prostacyclin, the major microvascular vasodilator and platelet antiaggregant, to platelet thromboxane A_2 (TxA_2), a powerful vasoconstrictor and platelet aggregant, has been suggested to be an important determinant of microvascular tone (Moncada, 1980). TxA_2 activity resides mainly in platelets and has been found to be consistently increased both in human diabetic neuropathy and in experimental diabetes. Prostacyclin activity, in contrast, resides almost exclusively in endothelial cells (Moncada and Vane, 1979; Weksler *et al.*, 1977). Some previous workers have demonstrated a reduction in prostacyclin production in diabetic vessels but almost all studies have focused on major vessels and on diabetes of recent onset. No studies have been reported on peripheral nerve. We therefore measured 6-keto-prostaglandin $F_{1\alpha}$ ($6KPGF_{1\alpha}$), the stable metabolite of prostacyclin, in the epineurium of rat sciatic nerve after 4 months of diabetes. Noradrenaline and $6KPGF_{1\alpha}$ were both reduced in sciatic nerve and may contribute the microvascular abnormalities in peripheral nerve in chronic streptozotocin diabetes in rats.

METHODS

Animals and induction of diabetes

We used Sprague Dawley male rats of initial weights of 130–140 g. These were then separated into two groups. Diabetic animals received an intraperitoneal injection of streptozotocin (STZ) in 0.05 M citrate buffer at pH 4.5 (65 mg/ml; dose 1.32 ml/kg). The control group received an intraperitoneal injection of citrate buffer alone. The rats were housed in cages with plastic floors covered with sawdust and wood shavings and were fed Purina rat chow (No. 5001) with an unrestricted supply of water. Rats were accepted as diabetic if fasting blood glucose exceeded 16.7 mmol/l 7 days after STZ and remained > 16.7 mmol/l at the time of harvest.

Electrophysiological methods

We used techniques that are standard for our laboratory. We measured sensory conduction velocity and nerve action potential amplitude in the caudal nerve (Low and McLeod, 1977; Low *et al.*, 1985) and sciatic-tibial motor nerve conduction velocity and the amplitude of the compound muscle action potential (Low and McLeod, 1977) using fine stainless steel near-nerve stimulating and recording electrodes. Recordings were done at 35° C and amplified × 1000, stored on digital tape and analysed off-line using a Nicolet 1170 digital oscilloscope (Nicolet Instruments, Madison, WI) with associated stimulators and stimulus isolation units.

Serum glucose

Serum glucose was determined using a glucose oxidase method as previously described (Low *et al.*, 1985). Measurements were done in duplicate at 450 nm on a LKB spectrophotometer (Ultraspec II).

Glycosylated haemoglobin (HbA_{1c})

Glycosylated haemoglobin was assayed by affinity column as previously described (Yue *et al.*, 1982, Tuck *et al.*, 1984).

Nerve noradrenaline determination

Tissue noradrenaline was determined using high performance liquid chromatography (HPLC) with electrochemical detection methodology. Wet weights expressed as means ±SD were as follows: 2.5±0.5 for control and 1.6±0.2 for diabetic ganglia; 9.3±1.2 for controls and 6.9±1.3 for diabetic sciatic nerve and 4.9±0.6 for controls and 3.0±0.7 for diabetic tibial nerves; n = 8 for each of the groups.

Nerve extract was prepared using the method of Chad *et al.* (1983), and measured using a modification of the method of Hegstrand and Eichelman (1981). Briefly, the tissue was homogenized in 0.1 M perchloric acid containing 0.1 mM ascorbic acid and 35 pg/μl dihydroxybenzylamine (the internal standard) then centrifuged. The supernate was then added to alumina to adsorb the catecholamines and washed three times with distilled water. The catecholamines were then eluted with acetic acid and injected into the HPLC column Electrochemical detection was performed on a BAS LC-4B detector set at 0.7 V. The mobile phase consisted of 0.1 M phosphate buffer pH 3.0 containing 0.2 mM octyl sulphonate, 0.1 mM EDTA and 6% methanol at a flow rate of 2 ml/min on an Altex Ultrasphere octyldecylsilane C18 column.

Nerve 6-keto-PGF$_{1\alpha}$ determination

Approximately 1 cm of tibial nerve was removed, desheathed, and the sheath and endoneurial contents separately weighed. The tissues were then minced and incubated in 0.5 ml of Krebs-Ringer bicarbonate buffer containing dextrose and previously gassed with 95% O_2/5% CO_2 for 1 h under an O_2-CO_2 (95/5%) atmosphere at 37° C. At the end of the incubation period, the tissue was homogenized in 1 ml ice-cold methanol and centrifuged at 12,000 *g* for 20 min at 4° C. After evaporation of the supernatant to dryness under nitrogen, the residue was resuspended in phosphate buffered saline (0.1 mol, pH 7.4 containing 1 mg/ml gelatine) and again centrifuged under the same conditions and the supernate stored until the radioimmunoassay (RIA).

Statistics

Statistical calculations were carried out on a Hewlett-Packard HP9845T computer with Data Manipulation and Basic Statistics, Regression, ANOVA and General Statistics programs. Values were expressed as mean ±SEM.

RESULTS

Animals

At onset the rats were well matched in weight. After 4 months of diabetes, however, animals had a lower weight, marked hyperglycaemia and increased glycosylated haemoglobin (Table 1).

TABLE 1. WEIGHTS AND GLYCAEMIC STATUS OF CONTROL AND DIABETIC RATS AFTER 4 MONTHS WITH DIABETES

Group	*n*	*Onset wt. (g)*	*Final wt. (g)*	*Blood glucose (mmol/l)*	*HbA$_{1c}$(%)*
Control	16	136±4	443±8	6.16±0.22	5.2±0.1
Diabetes	15	138±3	178±18*	27.20±0.83	16.2±0.6*

Results are expressed as mean ±SEM; * $P < 0.001$.

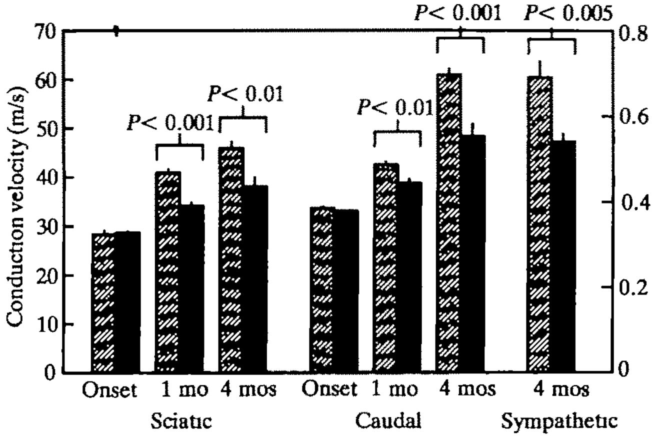

FIG 1. Nerve conduction studies on motor (sciatic-tibial), sensory (caudal) and sympathetic (cervical sympathetic chain) fibres. Closed columns (diabetes); hatched columns (control).

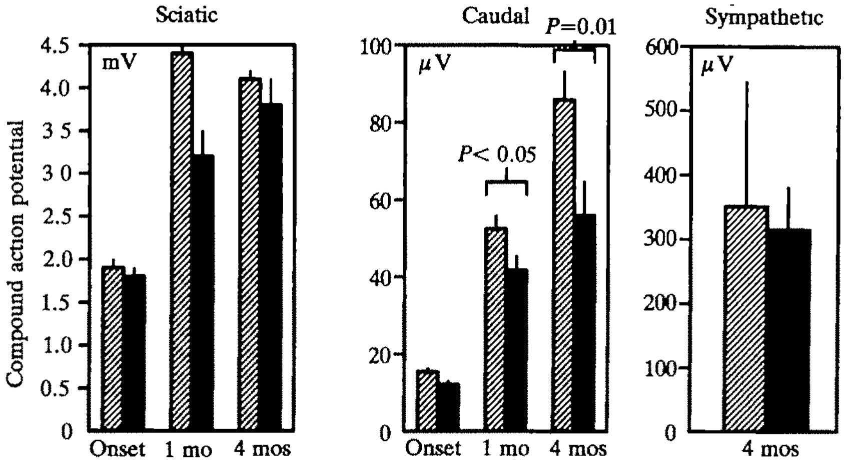

FIG 2. Compound action potentials on sciatic-tibial, caudal and cervical sympathetic chain nerves. Symbols as in fig. 1

Electrophysiology

Nerve conduction studies were performed on motor (sciatic-tibial), mainly sensory (caudal) and sympathetic (cervical sympathetic chain) fibres. Nerve conduction velocity was reduced in motor, sensory and sympathetic nerve fibres (fig. 1). Recordings were made at both the 1 and 4 months time-points in motor and sensory nerves and conduction velocity was slowed at both time-points. In the caudal nerve, conduction velocity progressively deteriorated with duration of diabetes and the nerve action potential was reduced in amplitude. The compound action potential was reduced in both sciatic-tibial and caudal nerves (fig. 2).

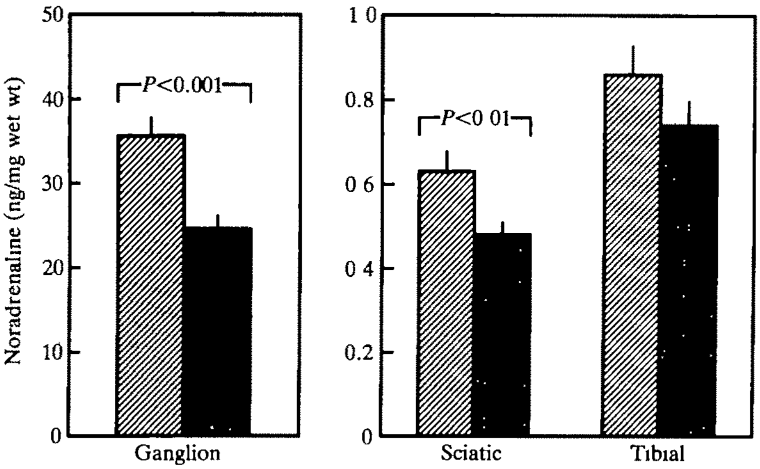

FIG 3. The noradrenaline content of control and diabetic tissues for cervical sympathetic ganglion, sciatic and tibial nerves. Closed columns (diabetes, 4 months); hatched columns (control).

Nerve noradrenaline (*NA*)

NA content was measured in cervical sympathetic ganglia, and the sciatic and tibial nerves. Initial experiments were done in which NA was separately measured in the nerve sheath and endoneurium. Although noradrenergic innervation is confined to the nerve sheath (Appenzeller *et al.*, 1984; Rechthand *et al.*, 1986), NA content was significantly higher ($P < 0.05$; Mann-Whitney U test) in the endoneurium (0.83 ± 0.09 ng/mg wet wt, n = 6) than in the sheath (0.39 ± 0.13 ng/mg wet wt, n = 5) and subsequent studies were done on whole nerve. The NA content was reduced by 31%, 24% and 18% for the cervical sympathetic ganglion, sciatic and tibial nerves (fig. 3).

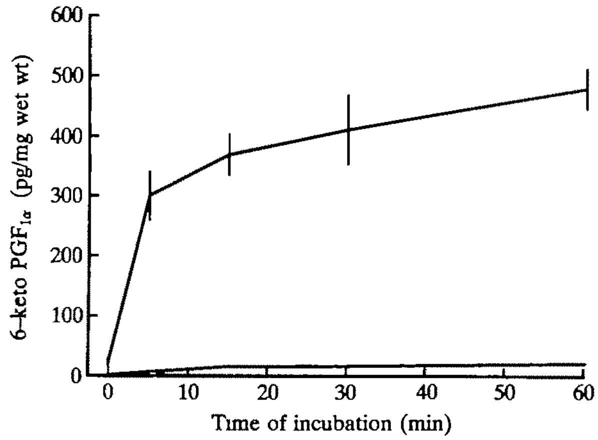

FIG 4 In vitro biosynthesis of 6-keto-prostaglandin $F_{1\alpha}$ of nerve sheath and endoneurium for different times of incubation.

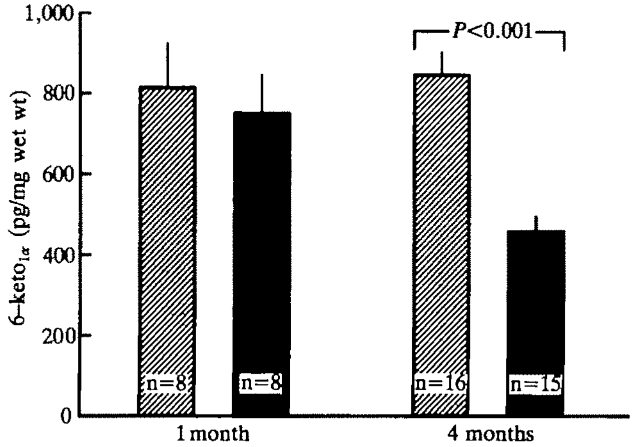

FIG. 5 Sciatic nerve biosynthesis of 6-keto-prostaglandin $F_{1\alpha}$ was unchanged after 1 month of diabetes; by 4 months the endogenous biosynthesis was reduced by 46% in diabetic nerves. Symbols as in fig. 1

Nerve 6-keto prostaglandin $F_{1\alpha}$ ($6KPGF_{1\alpha}$)

We separately determined the in vitro biosynthesis of $6KPGF_{1\alpha}$ in the nerve sheath and endoneurium for different times of incubation (fig. 4). The endogenous biosynthetic rate was 10–20 times greater in sheath than in endoneurium The rate was greatest in the first 15 min but continued for up to 1 h. In subsequent determinations we incubated the nerve sheath for 1 h.

At 1 month of diabetes, sciatic nerve biosynthesis of $6KPGF_{1\alpha}$ was unchanged; by 4 months the endogenous biosynthesis was reduced by 46% (fig. 5). The biosynthetic capacity of these nerves was examined by determining arachidonic acid stimulated biosynthesis of $6KPGF_{1\alpha}$. The nerves were incubated with 1 mM arachidonic acid for 5 min. The values following arachidonic acid stimulation were not increased at 1 month of diabetes but were markedly increased by 4 months (Table 2).

We also examined the effects of glucose concentration of the incubation medium and of insulin treatment on the in vitro biosynthesis of $6KPGF_{1\alpha}$ (Table 3). Experiments were done on control and diabetic animals after 1 month of diabetes. The higher glucose concentration had a mild nonsignificant depressant effect on

TABLE 2 NERVE 6-KETO-PROSTAGLANDIN $F_{1\alpha}$ IN CHRONIC EXPERIMENTAL DIABETES (4 MONTHS)

		6-keto prostaglandin $F_{1\alpha}$ *(pg/mg)*	
Group	*n*	*Endogenous*	*AA-stimulated*
Control	16	847±58	9999±1189
Diabetes	15	459±41*	24642±2623*

Results are expressed as mean ±SEM; * $P < 0.001$ AA = arachidonic acid.

TABLE 3 THE EFFECT OF ARACHIDONIC ACID (AA) OR GLUCOSE CONCENTRATION ON SCIATIC NERVE 6-KETO PROSTAGLANDIN $F_{1\alpha}$ ACTIVITY IN EXPERIMENTAL DIABETES (1 MONTH)

			Diabetic	
Parameter		*Controls*	*Untreated*	*Insulin*
Weight (g) end		343±9	203±10*	301±5*
Blood glucose (mmol/l)		5.66±0.17	24.92±1.16	17.10±1.28*
HbA_{1c}		4.2±0.1	16.7±0.5*	9.5±0.2*
$6KPGF_{1\alpha}$	6 mM glucose	814±113	751±97	1163±79
(pg/mg)	50 mM glucose	607±57	668±53	828±82
	1 mM AA	5410±550	6686±648	9043±1035

Results are expressed as mean ±SEM, * $P < 0.001$.

biosynthetic rate. Insulin-treated animals had a significant increase in $6KPGF_{1\alpha}$ biosynthesis.

DISCUSSION

The main electrophysiological finding was that abnormalities were present in all populations (motor, sensory and autonomic) of fibres studied. The motor abnormalities developed early (within 2 weeks of diabetes) in all experimental models of diabetes in the rat (Thomas and Eliasson, 1984). Electrophysiological abnormalities in the caudal nerve evolve more gradually and may more closely mimic human diabetic neuropathy (Low *et al.*, 1986). Little information is available on studies of the sympathetic system.

The main biochemical findings were a reduction in neural NA and of $6KPGF_{1\alpha}$ in chronic experimental diabetic neuropathy. The reduction in neural NA is not likely to be due to alterations in wet weight since we found that the water content in our chronically diabetic animals was not increased (65.6±0.7%, n = 6, in controls versus 64.5±1.4%, n = 7, in diabetics). The protein content per mg wet weight in preliminary work (expressed as mean ±SD) for controls was 92.1±11.7 μg/mg and 89.6±14.1 μg/mg for diabetics. The difference between controls and diabetics, the values expressed as NA/mg protein, is therefore likely to be identical. Dhital *et al.* (1986) found a similar reduction in NA content in sciatic nerve after 8 weeks of diabetes induced by streptozotocin. They found a similar reduction whether the results were expressed as NA/unit wet weight or per unit length so that the differences are unlikely to be due to an alteration in water content.

The reduction of endogenous biosynthesis of $6KPGF_{1\alpha}$ was related to the duration of diabetes, being absent at 1 month and markedly reduced after 4 months. There was a marked (2–3 fold) increase in arachidonic acid-stimulated generation of $6KPGF_{1\alpha}$, suggesting reduced substrate availability in vivo, with compensatory upregulation of cyclo-oxygenase and/or prostacyclin synthetase. Similar observations to ours were made in diabetic rat aorta (Roth *et al.*, 1983) and heart where altered regulation of phospholipase activity was suggested as the mechanism of reduced endogenous 6KPGF$_{1\alpha}$ (Rõsen *et al.*, 1983). One possible mechanism of reduced prostacyclin biosynthesis is the reduction of nerve NA. Noradrenaline release results in the increased synthesis and release of PGI$_2$ metabolites (Gilmore *et al.*, 1968) by an α-receptor-mediated and calcium/calmodulin-dependent mechanisms. Calmodulin is known to activate phospholipase A$_2$ (Wong and Cheung, 1979), resulting in a breakdown of membrane phospholipids to generate arachidonic acid (Burton *et al.*, 1986), whose availability is the rate limiting step in prostaglandin synthesis (Irvine *et al.*, 1982). NA may also be reduced by oxygen free radical generation, which is thought to be increased in chronic experimental diabetes (Karpen *et al.*, 1982) and may be generated from NA (Boveris and Chance, 1973).

These findings have implications on the pathogenesis of diabetic neuropathy. Microvascular pathology is present in human diabetic neuropathy and is the likely mechanism for the multifocal fibre loss characteristic of diabetic neuropathy (Timperley *et al.*, 1976; Johnson *et al.*, 1986; Yasuda and Dyck, 1987). Since nerve blood flow is reduced and endoneurial hypoxia is present by 4 months of experimental diabetic neuropathy (Low *et al.*, 1984; Tuck *et al.*, 1984), the microvascular pathology is likely to be of pathogenetic importance rather than a late incidental change. Chronic hyperglycaemia has been suggested to cause macro- and microvascular atherogenesis by the generation of advanced glycosylation end-products. The latter, by increasing macrophage recognition and uptake, stimulates macrophage-derived growth factor comprising one mechanism which has been suggested to result in smooth muscle proliferation and atherogenesis (Vlassara *et al.*, 1986). Our present results suggest the superimposition of an ischaemic-hypoxic cycle whereby once hypoxia is established it activates a vicious cycle of further capillary damage and escalating hypoxia (fig. 6).

Endoneurial ischaemia-hypoxia results in the breakdown of ATP (Low *et al.*, 1985), eventually to hypoxanthine and the generation of reducing equivalents including NADPH (Neely *et al.*, 1981; Low *et al.*, 1985), and conversion of xanthine dehydrogenase to xanthine oxidase, its active form (McCord, 1985). The availability of substrate, enzyme and cofactor would create an in vivo free radical generating system (McCord, 1985) generating the superoxide radical. Intermittent ischaemia may be more deleterious since reperfusion results in accelerated free radical formation by introducing oxygen into a system that has been primed and producing free radicals (McCord, 1985). Superoxide radical is converted to hydrogen peroxide by superoxide dismutase, which is reduced in some diabetic tissues (Crouch *et al.*, 1978). The superoxide generated may reduce metal chelates by the Haber-Weiss reaction to generate hydroxyl radicals (Freeman and Crapo, 1982) which damage endothelial cells. The blood-nerve barrier has been reported to be defective in both human (Ohi *et al.*, 1985) and experimental diabetes

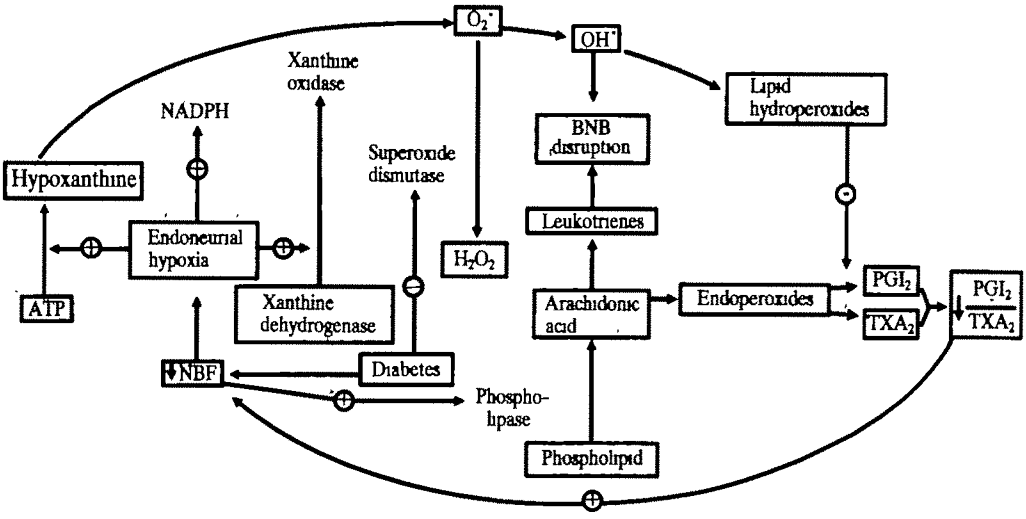

FIG. 6 Proposed ischaemic-hypoxic cycle (*see* text for details)

(Rechthand *et al.*, 1987). Oxygen-free radicals react with several compounds including lipids to generate lipid hydroperoxides. Ischaemia will activate phospholipases especially A_2 (Bazán, 1970) to break down membrane phospholipids and activate the arachidonic acid cascade generating leukotrienes (further damaging endothelial cells) and prostaglandins (Wolfe, 1982). Prostacylin is the major vasodilator and inhibitor of platelet aggregation and thromboxane A_2 has the opposite effects. The ratio of prostacyclin to thromboxane A_2 is considered to be important in the maintenance of vascular tone (Moncada and Vane, 1979). Lipid hydroperoxides increase cyclo-oxygenase activity (Hemler *et al.*, 1979) but inhibit prostacyclin synthetase activity (Moncada *et al.*, 1976) so that the prostacyclin: thromboxane ratio is reduced, favouring vasoconstriction and platelet aggregation in diabetes, further aggravating microvascular ischaemia-hypoxia. An increase in platelet thromboxane synthesis has been consistently found in human and experimental diabetes (Ziboh *et al.*, 1979; Gerrard *et al.*, 1980; Halushka *et al.*, 1981; Karpen *et al.*, 1982) and plasma TxB_2 synthesis regresses with plasma glucose (Rechthand *et al.*, 1986). Prostacyclin is produced almost entirely in microvessels. The marked reduction in peripheral nerve $6KPGF_{1\alpha}$ in conjunction with the known increase in platelet TxB_2 would result in vasoconstriction and susceptibility to platelet aggregation and adhesion, resulting in further ischaemia, hypoxia and capillary damage.

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X-LINKED RECESSIVE BULBOSPINAL NEURONOPATHY

A CLINICOPATHOLOGICAL STUDY

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SUMMARY

A clinicopathological study on X-linked recessive bulbospinal neuronopathy was undertaken on 9 cases, with morphological observations on 3 autopsied cases and sural nerve biopsies from 6 patients. Both lower motor and primary sensory neurons were involved. Lower motor neurons were markedly depleted through all spinal segments and in brainstem motor nuclei except for the third, fourth and sixth cranial nerves. Primary sensory neurons were less severely affected. A quantitative study of primary sensory axons at several levels in the peripheral nervous system suggested that a distally accentuated axonopathy was the salient pathological process. Segmental demyelination and remyelination clustered on individual fibres, and g ratios (axon diameter : total fibre diameter) in the sural nerve showed an increased scatter in some cases. Evidence of regeneration was inconspicuous. Unmyelinated fibres were well preserved throughout all the nerves examined. Neurons in the Onufrowicz nuclei, in the intermediolateral columns and in Clarke's columns of the spinal cord were generally well preserved. These observations indicate that a lower motor and primary sensory neuronopathy is a major neurological manifestation in this disease.

INTRODUCTION

X-linked recessive bulbospinal neuronopathy is characterized by adult onset proximal muscular atrophy, bulbar involvement, marked contraction fasciculation, and very slow progression. Several early reports have described clinical, genetic and pathological aspects of this disease (Takikawa, 1953; Magee, 1960; Tsukagoshi *et al.*, 1965; Gross, 1966).

In 1968, Kennedy *et al.* reported 11 males from two families and described this disease as a distinctive form of adult onset spinal muscular atrophy with X-linked recessive inheritance. Since then, many families with a similar disease have been described (Stefanis *et al.*, 1975; Ringel *et al.*, 1978; Schoenen *et al.*, 1979; Paulson

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et al., 1980; Barkhaus *et al.*, 1982; Harding *et al.*, 1982; Arbizu *et al.*, 1983; Hausmanova-Petrusewicz *et al.*, 1983; Martinelli *et al.*, 1986; Evans *et al.*, 1987; Wilde *et al.*, 1987), especially from Japan (Araki *et al.*, 1966; Shoji *et al.*, 1970; Tsukagoshi *et al.*, 1970; Araki and Ushio, 1972; Imai *et al.*, 1980; Mukai, 1980; Mukai and Sobue, 1980; Mukai *et al.*, 1981; Ozaki *et al.*, 1981; Usuki *et al.*, 1982; Nagashima *et al.*, 1984, 1987). Slowly progressive bulbar signs, proximal muscular atrophy with prominent fasciculation and tremor are common to all these reports. Gynaecomastia, hepatic involvement, a high incidence of diabetes mellitus, abnormalities in serum sex hormone levels, and testicular atrophy have been noted in some patients (Kennedy *et al.*, 1968; Imai *et al.*, 1980; Mukai and Sobue, 1980; Harding *et al.*, 1982; Usuki *et al.*, 1982; Arbizu *et al.*, 1983; Hausmanova-Petrusewicz *et al.*, 1983), and some of these abnormalities are considered to be of genetic origin. The gene locus responsible for this disease was recently found to be linked to the DXYSI marker on the proximal long arm of the X chromosome (Fischbeck *et al.*, 1986*b*).

Harding *et al.* (1982) described 10 cases of this disease and found reduced or absent sensory nerve action potentials in 6 cases, indicating that this disease is not pure degeneration of brainstem and spinal motor neurons. Wilde *et al.* (1987) reported electrophysiological and sural nerve biopsy findings from 3 patients and confirmed Harding's description. X-linked recessive bulbospinal neuronopathy is now considered to be a multisystem disease, involving both the endocrine system, and sensory afferent and motor efferent neurons.

So far, 5 autopsied cases have been reported (Magee, 1960; Kennedy *et al.*, 1968; Paulson *et al.*, 1980; Mukai *et al.*, 1981; Nagashima *et al.*, 1987), but the nature of the pathology, especially of the sensory afferent system, has not been well characterized. In this report, we describe clinicopathological findings in 3 autopsied cases and 6 sural nerve biopsies from independent family pedigrees, and document the nature of the neuropathological process in this disease.

PATIENTS AND METHODS

Five of the 9 patients had a familial history as shown in fig. 1. The other 4 patients had no apparent familial history of similar disease.

Electrophysiology

Motor and sensory conduction velocities were measured by the methods of Buchthal and Rosenfalck (1966), Buchthal and Behse (1971), and Kimura (1984), respectively. Motor nerve conduction velocity (MCV) was examined in the median, ulnar and tibial nerves on recording from the abductor pollicis brevis, abductor and flexor digiti minimi, and flexor hallucis brevis, respectively. Sensory nerve conduction velocity (SCV) was examined in the median nerve on stimulation of the digital nerves of digit II with recording at the wrist, in the sural nerve on stimulation on the dorsum of the foot with recording at the lateral malleolus. The sensory action potentials were recorded by electronic averaging of 20 to 256 responses.

Electromyography, using a concentric needle electrode, was performed in the biceps brachii, brachioradialis, thenar, hypothenar, quadriceps femoris and anterior tibial muscles.

Values for nerve conduction velocity and nerve amplitude were compared with the normal values reported by Buchthal and Rosenfalck (1966), Behse and Buchthal (1971) and Kimura (1984).

Histopathology

Whole sural nerve biopsy was performed at the level of the lateral malleolus under local anaesthesia in 6 patients. The specimens were fixed in 2% glutaraldehyde in 0.1 M phosphate buffer, and processed for teased fibre studies and semithin or ultrathin section (Sobue *et al.*, 1981*b*, 1986*a*, *b*). Muscle biopsy specimens were obtained from the vastus medialis or deltoid, fixed in 10% buffered formalin, and embedded in paraffin or frozen in isopentane-dry ice for histochemical analysis of myosin-ATPase (Koga *et al.*, 1985)

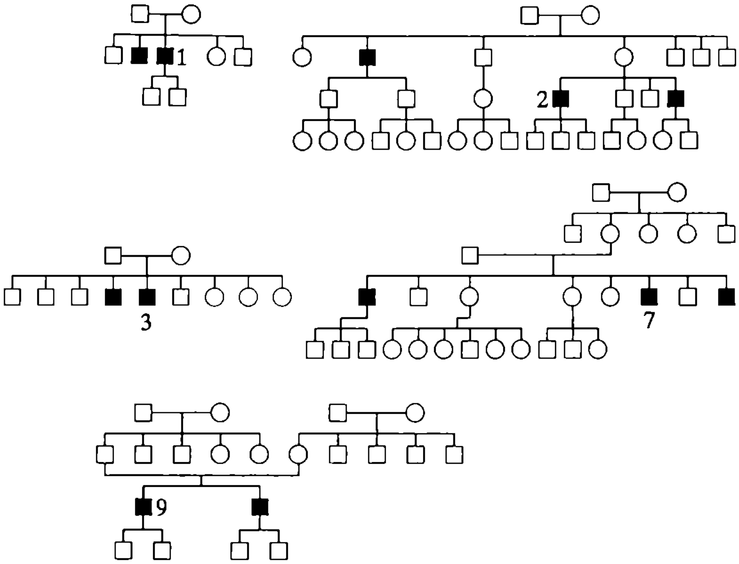

FIG. 1. Family pedigrees of Cases 1, 2, 3, 7, and 9

Brain, whole spinal cord, dorsal root ganglia from L2 to L4 and muscles from upper and lower limbs from autopsied cases were fixed in 10% buffered formalin and embedded in paraffin. Sections were generally stained with haematoxylin and eosin, and with Klüver-Barrera, Holzer and Bodian in some cases.

In 2 autopsied cases, the fasciculus gracilis at T7 level, ventral spinal roots of all spinal levels and C6, T7, L4, L5, S1 dorsal roots, femoral nerve, two different levels of the sciatic nerve (middle and lower thirds) and distal branches of the tibial and sural nerves were removed and were fixed in 2% glutaraldehyde in 0.1 M phosphate buffer, postfixed in 2% osmium tetroxide in the same buffer and processed for semithin and ultrathin sections.

The density of myelinated fibres was calculated from photographs at a magnification of × 1,000 of toluidine blue-stained semithin sections by using a particle size analyser (Zeiss TGZ-3) as described previously (Kawamura and Dyck, 1977, Kawamura *et al.*, 1977; Dyck *et al.*, 1978, 1984; Sobue *et al.*, 1981*b*, 1986*a*, 1987). The fascicular area was estimated on the photographs at a magnification of ×200 using a computer-assisted image analyser (Kontron Videoplan), g ratios (ratio of axonal to fibre diameter) were calculated assuming axonal circularity (Karnes *et al.*, 1977).

Isolated single nerves were prepared from specimens obtained at various levels, and the pathological condition of each fibre was evaluated according to previously described criteria (Dyck and Lais, 1973; Dyck *et al.*, 1978, 1984; Matsuoka *et al.*, 1981). To assess clustering of demyelinated and remyelinated internodes on individual fibres, prepared teased fibres were numbered sequentially as they were prepared. According to the criteria described by O'Brien (1976) and Dyck *et al.* (1977), an intact old internode was identified as a plus, and regions corresponding to internodes having varying combinations of demyelination and remyelination were scored as a minus. Results obtained in this way were analysed using a computer-assisted system described by O'Brien (1976).

RESULTS

Clinical and electrophysiological studies

The pedigrees (fig. 1) of the 5 patients with relatives were consistent with X-linked recessive inheritance. The remaining 4 patients were single cases. The clinical features of the 9 patients are summarized in Table 1. Three cases, in which postmortem examination was performed, are described in more detail.

The age of the patients ranged from 51 to 72 yrs. In most, the initial symptom was fine finger tremor, which appeared in the middle of the third decade. Gynaecomastia was seen in 6 patients. Contraction fasciculation was common in all and occurred in facial, trunk and limb muscles. Dysphagia was present in all, was generally mild, but occasionally became troublesome later in the clinical course. Muscle atrophy and weakness were prominent in the tongue and proximal upper and lower limbs. The tendon reflexes were absent in 7 cases, but in 2 they were well preserved proximally in the limbs. An extensor plantar response was noted on one side of a hemiplegic patient (Case 6). Sensory involvement was largely restricted to vibration sense which was impaired distally in the legs in all cases in varying degree. In the upper limbs, impairment in vibration sense was seen in 6 out of the 9 cases, but was minimal. Although sensation for position and light touch was mostly preserved, 3 patients showed slight impairment for touch, pain and position as well as for vibration distally in the lower or upper limbs. Serum CK levels were elevated in 8 out of the 9 patients (Table 1) up to eight times above normal values. The cerebrospinal fluid was examined in 8 cases and was normal in all. Two patients showed disturbances of micturition with slowness of initiation apparently not related to prostate hypertrophy. One patient had severe constipation, which occasionally developed into paralytic ileus, and 3 patients had dryness of the skin in the distal extremities. Three patients had a mild to moderately impaired glucose tolerance. Three showed a mild elevation of serum glutamic-pyruvic transaminase activity.

The results of electrophysiological studies are summarized in Table 2. Motor nerve conduction in the median and ulnar nerves was almost within normal limits, but the posterior tibial and peroneal nerves showed borderline or slightly reduced values. Terminal motor latencies, however, were prolonged, even in the patients with normal motor conduction. Sural nerve action potentials were absent in 4 patients and a reduction in amplitude was noted in all other recordings of median

TABLE 1. CLINICAL FEATURES

					Muscle atrophy			
Case	*Age (yrs)*	*Gynaecomastia*	*Contraction fasciculation*	*Dysphagia*	*Facial*	*Tongue*	*Proximal upper limb*	*Distal upper limb*
1	51	0	++	+	+	+	+	+
2	72	0	++	+	+	++	++	+
3	59	+	++	+	++	+++	++	+
4	69	+	++	+	+	+++	++	++
5	62	+	++	±	±	++	++	+
6	58	+	++	+	±	++	++	+
7	57	+	++	+	±	+	++	++
8	59	+	++	±	0	+	++	+
9	52	0	++	±	+	++	+	+

	Muscle weakness		Muscle weakness					Tendon reflexes			
	Proximal lower limb	*Distal lower limb*	*Tongue*	*Proximal upper limb*	*Distal upper limb*	*Proximal lower limb*	*Distal lower limb*	*Biceps brachii*	*Brachioradialis*	*Knee*	*Ankle*
1	+++	++	++	++	++	+++	++	A	A	A	A
2	++	++	++	++	++	+++	+++	A	A	A	A
3	++	++	++	+++	++	++	++	A	A	A	A
4	++	++	++	++	++	++	±	N	D	N	D
5	++	++	+	++	+	++	+	A	A	A	A
6	++	+	++	++	+	++	+	N	A	N	A
7	++	++	+	++	++	++	++	A	A	A	A
8	++	++	+	+	+	++	++	A	A	A	A
9	++	+	+	++	+	++	+	A	A	A	A

	Sensory impairment							
	Upper limbs			Lower limbs				
	Vibration	*Position*	*Pain-touch*	*Vibration*	*Position*	*Pain-touch*	*Serum CK*	*Diabetic pattern in GTT*
1	0	0	0	+	0	0	170 (20–100)	
2	±	0	0	+	0	0	209 (21–107)	+
3	0	0	0	+	0	+	507 (20–110)	+
4	+	0	0	+	0	0	150 (30–170)	
5	0	0	0	±	0	0	245 (30–170)	
6	±	0	0	+	0	0	433 (30–170)	+
7	+	+	+	++	+	+	763 (21–107)	
8	±	±	±	++	+	+	187 (20– 80)	
9	±	0	0	+	0	0	1460 (30–170)	

+ = abnormal; A = absent; D = decreased, N = normal, CK = serum creatine kinase, normal range (IU/ml) in brackets and sural sensory nerve action potentials. Electromyographic abnormalities, with reduced motor unit recruitment patterns, polyphasic units of long duration and increased amplitude (greater than 5 mV) were common in all patients. Positive sharp waves and fibrillation were also frequent.

TABLE 2. ELECTROPHYSIOLOGICAL FEATURES

	Motor conduction ($m \cdot s^{-1}$)				*Distal latency* (*ms*)			
Case	*Median*	*Ulnar*	*Tibial*	*Peroneal*	*Median*	*Ulnar*	*Tibial*	*Peroneal*
1	—	—	51 4	—	—	—	—	—
2	59.6	66.5	40 1	—	5.6	5 2	5.2	—
3	—	—	—	—	—	—	—	—
4	52.7	51.2	34.6	35.3	4 3	3.5	6.4	8.8
5	52.5	—	40.4	—	—	—	—	—
6	56.0	60 3	42.6	—	4.4	3.0	3.9	—
7	51 7	50.0	38.5	—	4.9	3.3	5.1	—
8	—	—	51.4	—	—	—	—	—
9	48.7	51.5	43.8	—	5.1	3.7	5.2	—

	Sensory conduction ($m \cdot s^{-1}$)		*Sensory action potential* (μV)	
	Median	*Sural*	*Median*	*Sural*
1	57.1	—	—	—
2	61 2	43.6	13.8	1.8
3	—	—	—	—
4	42 2	A	3.8	A
5	43.3	A	1.4	A
6	47.2	A	3 3	A
7	40.2	A	—	A
8	57.1	—	—	—
9	47.3	40.4	2.2	3.6

A = absent.

CASE REPORTS

Case 1

A 51-yr-old businessman noticed a fine tremor in his hands and fingers when aged 27 yrs. He became unable to run from the middle of the fourth decade, and later noted weakness of the upper limbs. On examination at the age of 50 yrs, he had slight weakness and atrophy of the facial and masseter muscles, and marked atrophy and fasciculation of the tongue. Slight dysarthria and dysphagia were noted. There was prominent bilateral weakness and atrophy in the proximal portions of the limbs as well as in the shoulder and limb girdle musculature. Contraction fasciculation was marked. The tendon reflexes were all absent. Vibration sense was impaired in the distal portions of the legs but not in the upper limbs. Sensation other than vibration was preserved. There was no gynaecomastia. He died at the age of 51 yrs from bronchopneumonia and emphysema confirmed at autopsy.

Case 2

A 72-yr-old man had been aware of difficulty in whistling and in sucking up noddles when eating from the middle of his third decade. He noticed fine tremor in the perioral region and in his fingers at the age of 39 yrs. Slight dysarthria was seen at this stage. From his mid-fifties he noticed slowly progressive difficulty in climbing stairs. On examination in 1978 when he was aged 68 yrs, mild to moderate muscle wasting was present bilaterally in the facial, masseter, sternomastoid and tongue muscles, together with slight dysphagia and dysarthria. There was moderate to marked proximal muscle weakness and atrophy bilaterally. In the legs, flexor muscles were more severely affected than extensors with marked contraction fasciculation. Vibration sense was moderately impaired in the feet and slightly in the fingers. The tendon reflexes were all absent. There was tremor in the outstretched hands and when writing. There was no gynaecomastia. In 1980 he developed carcinoma of the rectum with liver metastasis. This was treated by chemotherapy. Neurological examination revealed no substantial change. In 1984 he was admitted with general emaciation, jaundice and an upper respiratory tract infection. Autopsy showed papillocystic adenocarcinoma in the rectum and multiple large metastases in the liver, with marked biliary stasis.

Case 3

A 59-yr-old man had noticed weakness of the arms in the beginning of his fourth decade. When aged 47 yrs, difficulty in walking appeared. He also noticed fasciculation in his facial muscles and finger tremor. On neurological examination at the age of 59 yrs he showed hoarseness and dysarthria, muscle weakness and atrophy in the face, tongue, and upper and lower limbs with prominent contraction fasciculation. The tendon reflexes were absent. Mild sensory impairment for vibration and in pin prick was present distally in both legs. Bilateral gynaecomastia, slight hepatic dysfunction manifested by increased serum transaminase levels, and intolerance to oral glucose loading were seen. From the age of 53 yrs the patient had had dysphagia which, at the age of 59 yrs resulted in a fatal aspiration pneumonia. At autopsy, bronchopneumonia with a large abscess was found in the left lung.

PATHOLOGICAL FINDINGS

Posterior columns of the spinal cord, dorsal roots and dorsal root ganglia

Myelin pallor in the fasciculus gracilis was observed in the 3 autopsied cases. This myelin pallor was more prominent in the more rostral than the more caudal segments of the spinal cord (fig. 2). Morphometric analysis revealed marked myelinated fibre loss in 2 cases (Table 3). Holzer staining, however, did not show significant reactive gliosis.

Dorsal spinal roots at various spinal segmental levels showed normal findings on light microscopy (fig. 3). The fourth lumbar dorsal spinal roots from 2 cases were examined morphometrically and there was almost no alteration in fibre population and fibre size distribution as compared with normal controls (fig. 4). Teased fibre preparations, however, revealed a considerable increase in fibres with segmental demyelination and remyelination, frequently clustered along a single fibre (fig. 5). On statistical analysis of teased fibre preparations using O'Brien's method (1976), χ^2, degrees of freedom and P values were obtained as 117.8, 29.0, < 0.0001 for Case 1 and 86.9, 36.0, < 0.0001 for Case 2, respectively. These results indicate that there is a highly significant departure from randomness in the distribution of demyelination or remyelination.

The third and fourth lumbar dorsal root ganglia were examined in 2 autopsied cases (fig. 6). Residual nodules of Nageotte and proliferation of capsule cells were

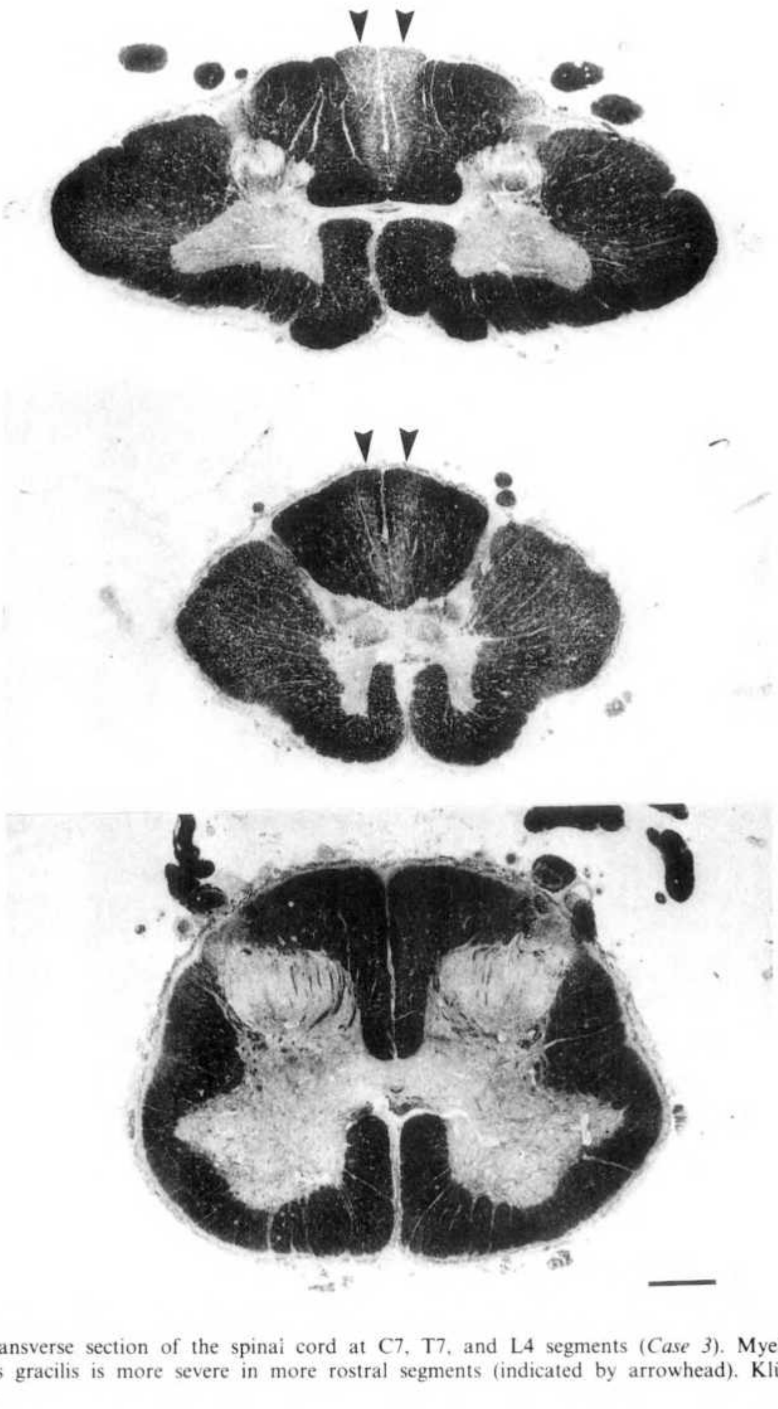

FIG. 2. Transverse section of the spinal cord at C7, T7, and L4 segments (*Case 3*). Myelin pallor in the fasciculus gracilis is more severe in more rostral segments (indicated by arrowhead). Klüver-Barrera. Bar = 1 mm.

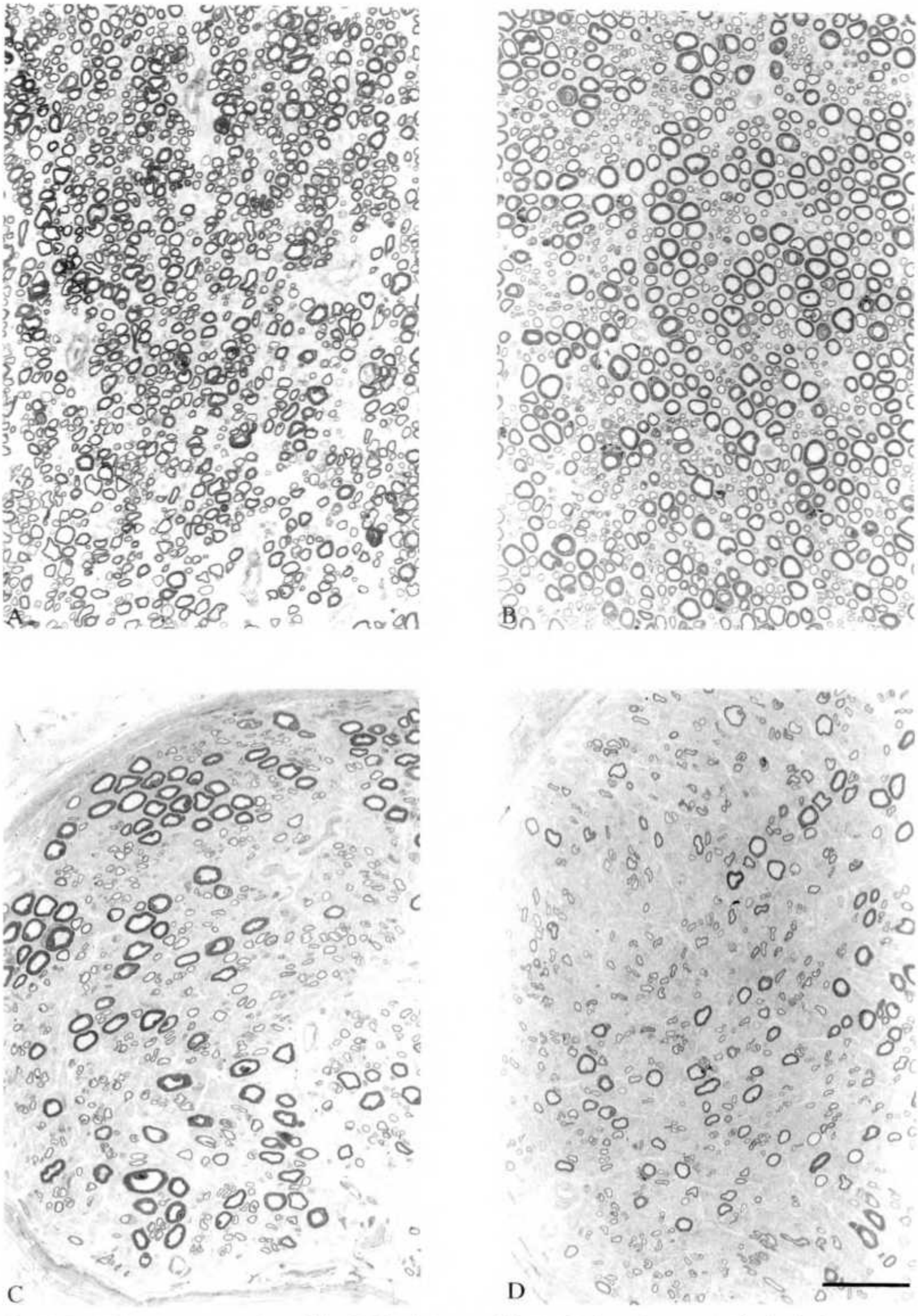

FIG. 3. Semithin transverse section of the T7 fasciculus gracilis (A), L4 dorsal roots (B), distal sciatic nerves (C), and sural nerves (D) (*Case 2*). Toluidine blue. Bar = 45 μm, same magnification in A–D).

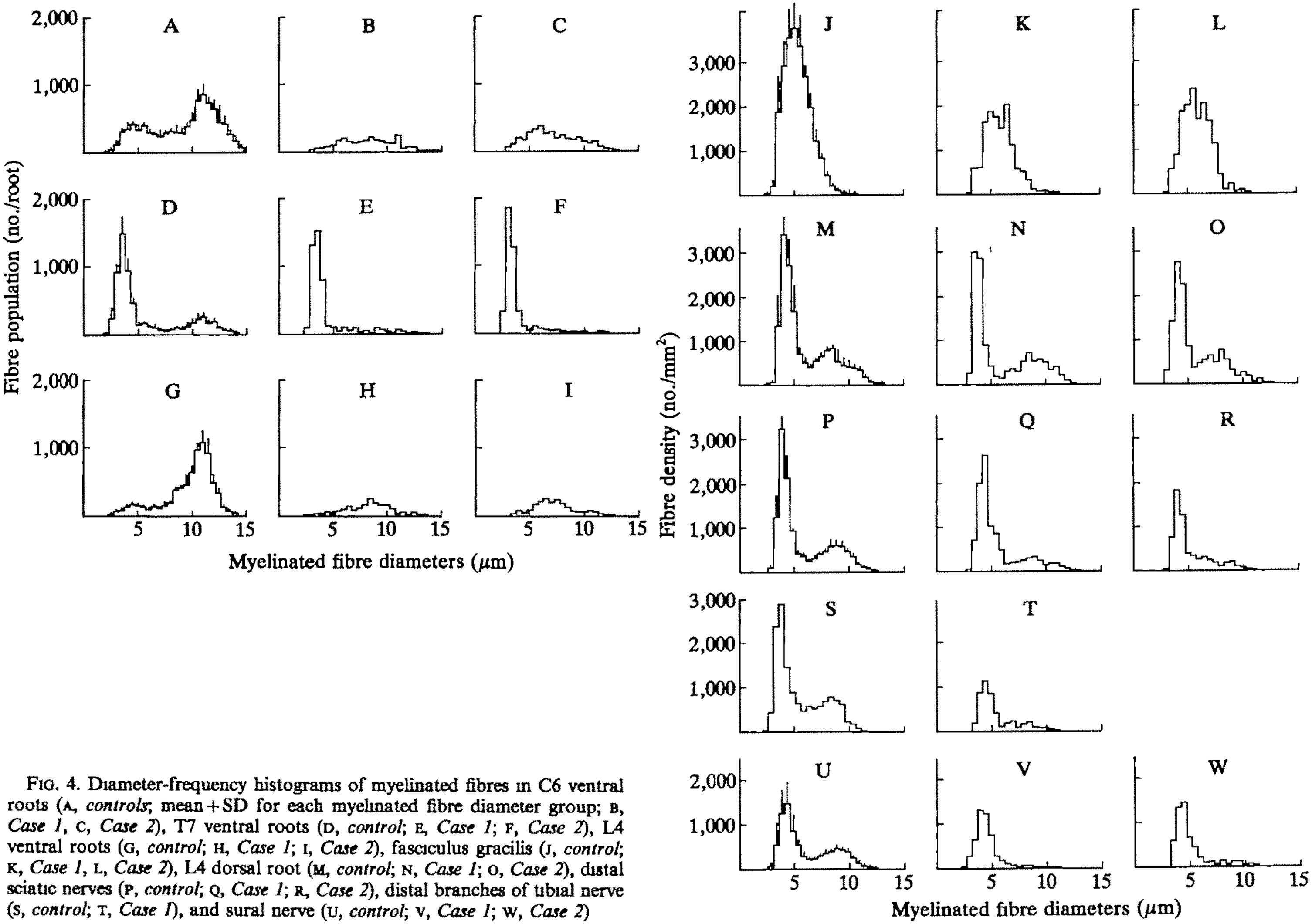

FIG. 4. Diameter-frequency histograms of myelinated fibres in C6 ventral roots (A, *controls*; mean+SD for each myelinated fibre diameter group; B, *Case 1*, C, *Case 2*), T7 ventral roots (D, *control*; E, *Case 1*; F, *Case 2*), L4 ventral roots (G, *control*; H, *Case 1*; I, *Case 2*), fasciculus gracilis (J, *control*; K, *Case 1*, L, *Case 2*), L4 dorsal root (M, *control*; N, *Case 1*; O, *Case 2*), distal sciatic nerves (P, *control*; Q, *Case 1*; R, *Case 2*), distal branches of tibial nerve (S, *control*; T, *Case 1*), and sural nerve (U, *control*; V, *Case 1*; W, *Case 2*)

TABLE 3 QUANTITATIVE STUDIES ON MYELINATED FIBRES IN TWO AUTOPSIED CASES

	Case 1				*Case 2*				*Controls*		
	Small	*Large*	*Total*	*% Large fibres*	*Small*	*Large*	*Total*	*% Large fibres*	*Small*	*Large*	*Total*
Cranial nerve roots*											
III	6828	12546	19374	83.5					7412 ± 101(5)	15032 ± 178(5)	22444 ± 1669(5)
IV	914	1623	2537	99.3					1215 ± 204(5)	1634 ± 194(5)	2849 ± 216(5)
VI	1458	5333	6791	107.7					1983 ± 202(5)	4950 ± 202(5)	6933 ± 428(5)
Ventral spinal roots*											
C6a	1005	1161	2166	17.9	1617	1602	3219	24.7	1950 ± 341(3)	6494 ± 1005(3)	8444 ± 1111(3)
T7A	4068	612	4680	36.5	3974	315	4289	18.8	4433 ± 399(3)	1676 ± 320(3)	6109 ± 518(3)
L4A	444	1016	1460	16.3	952	1117	2069	17.9	1121 ± 623(3)	6220 ± 426(3)	7341 ± 278(3)
Fasciculus gracilis at T7**			12826				16618				24408 ± 2034(4)
Dorsal spinal root L4P**	9244	3872	13116	74.2	8349	5250	13599	100.5	11273 ± 2312(5)	5223 ± 313(5)	16496 ± 2158(5)
Distal sciatic**	7793	1949	9742	45.8	5784	1534	7318	36.0	8703 ± 323(4)	4257 ± 264(4)	12960 ± 343(4)
Distal tibial**	3792	1071	4863	28.3					9776	3788	13564
Sural**	5345	388	5733	12.6	5153	805	5958	26.2	5122 ± 438(4)	3068 ± 2941(4)	8190 ± 511(4)

* Number of myelinated fibres per root. ** Density of myelinated fibres per mm². Small = < 6.73 μm, Large = ≧ 6.73 μm, controls are expressed as mean ± SD for the number of cases indicated in brackets. % large fibre: ratio of large myelinated fibre density or population to mean value of control large fibre density or population expressed as a percentage.

TABLE 4 TEASED FIBRE STUDIES

Case	*Normal appearances*	*Axonal degeneration and regeneration*	*Segmental demyelination and remyelination*
Sural nerves			
1	93	0	7
2	89	5	6
3	—	—	—
4	93	4	3
5	84	0	16
6	84	4	12
7	—	—	—
8	85	3	12
9	79	2	19
Controls (n = 6)	95.8±2.8 (92–100)	0.5±0.8 (0–2)	3.8±2.2 (0–6)
Fourth lumbar ventral roots			
1	96	0	4
2	92	2	6
Controls (n = 6)	95.4±3.2 (90–100)	0.3±0.7 (0–2)	4.3±3.1 (0–10)
Fourth lumbar dorsal roots			
1	74	0	26
2	68	2	30
Controls (n = 2)	92.5	0	7.5

Control values are expressed as mean ± SD with the range of values in brackets for the number of cases indicated

rarely seen in either case. No substantial neuronal loss was observed in these 2 cases.

Femoral, sciatic, tibial and sural nerves

The proximal femoral nerve, the sciatic nerve at midthigh level and just above its bifurcation, and distal tibial nerve from 2 autopsied cases, together with sural nerves from 8 cases, were examined quantitatively. Myelinated fibre populations in the femoral nerve were well preserved, but a definite reduction was observed in sciatic, tibial and sural nerves (figs 3, 4). There was a proximal to distal gradient of myelinated fibre loss, particularly for large myelinated fibres, in the sciatic nerve and its branches (figs 3, 4, Table 3). In the sural nerve, there was also a marked reduction of myelinated fibres mainly for those of large diameter (figs 3, 4, Tables 3, 5). Fibre size-frequency histograms in the sural nerve were nearly unimodal (fig. 4) as a result of the loss of large myelinated fibres. Regeneration clusters were rarely seen at any level.

Axon swellings with an abnormal accumulation of neurofilaments and organelles as reported by Wilde *et al.* (1987) were rarely seen in our patients. Outpouching of myelin into the Schwann cell cytoplasm of myelinated fibres was frequently observed, together with separated ovoids of myelin containing axonal or

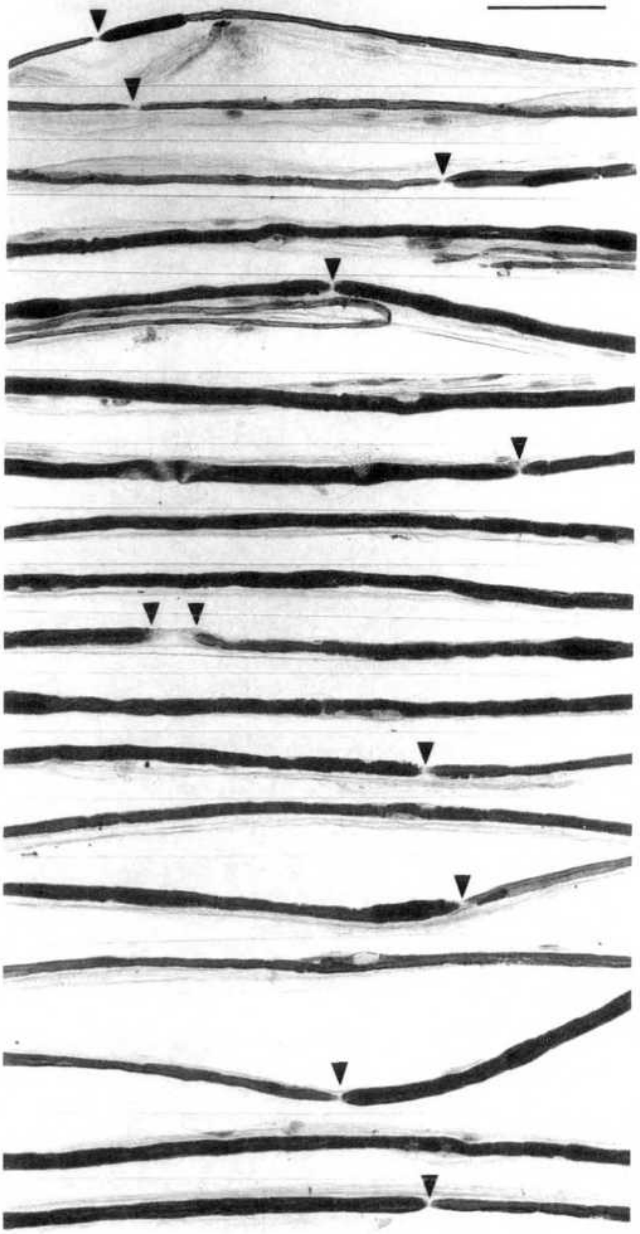

FIG. 5. Consecutive portions along the length of a single teased fibre from L4 dorsal root in *Case 2*. Multiple remyelinated internodes are seen. Osmium tetroxide. Bar = 40 μm.

cytoplasmic debris. Hypertrophic changes were rarely observed. The density of unmyelinated fibres in the sural nerve is given in Table 5 and was indistinguishable from controls. Their appearances were normal at all levels.

Teased fibre studies showed a slight but definite increase in the incidence of

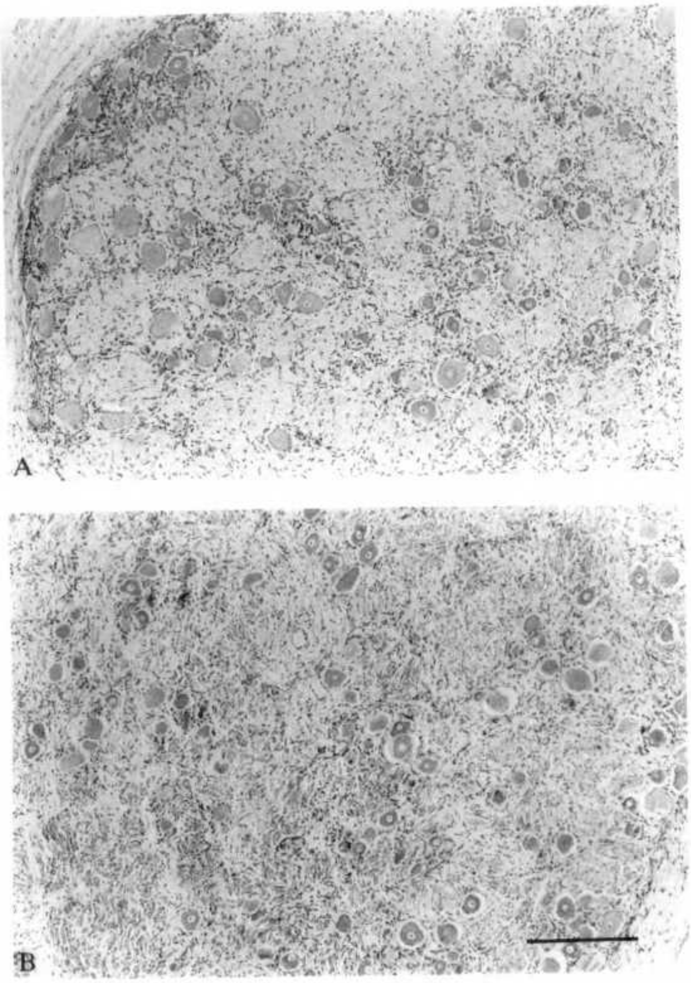

FIG. 6. Lumbar posterior root ganglia from *control* (A), and *Case 1* (B). Neuronal cells are well populated and proliferation of capsule cells and residual nodules of Nageotte are rarely seen. Klüver-Barrera. Bar = 265 μm, same magnification in A, B.

fibres with segmental demyelination and remyelination in the sural nerves in most cases. Segmental abnormalities of the myelin sheath were frequently clustered along individual fibres. The scattergrams for g ratios (axon diameter : total fibre diameter) of myelinated fibres from the sciatic nerves from 2 cases were not significantly different from controls, but those from the sural nerves in some of the cases showed a greater scatter as compared with controls (fig. 7, cf. Jacobs and Love (1985)).

Ventral spinal roots and ventral horn cells

A marked loss of large myelinated fibres was evident through all the spinal segments (fig. 4). There was no apparent gradient in rostral-caudal distribution of fibre loss in terms of spinal segments (fig. 8). The roots were well populated with small myelinated fibres (figs 4, 8). In particular, the distinctive sharp peak in the fibre-size histograms in thoracic (fig. 4) and sacral segments corresponding to autonomic preganglionic fibres was preserved. Clustering of small myelinated fibres suggesting axonal regeneration was rarely seen. Teased fibre preparations of myelinated fibres showed only a few active degenerating fibres with myelin ovoids and segmental demyelination and remyelination (Table 4). There was a marked depletion of ventral horn cells, particularly in the lateral nuclear groups, through all spinal segments. Simple atrophy of neurons was observed, but central chromatolysis and neuronophagia were seldom seen. Reactive astrogliosis was also slight.

TABLE 5. QUANTITATIVE DATA FOR SURAL NERVE BIOPSIES

	Myelinated fibre density (no./mm^2)				*Unmyelinated fibre density (no./mm^2)*
	Small	*Large*	*Total*	*% Large fibres*	
Case 4	5748	1039	6787	33.9	33455
Case 5	3983	601	4584	19.6	32426
Case 6	5965	764	6729	24.9	38099
Case 7	4617	821	5438	26.8	—
Case 8	—	—	—	—	—
Case 9	6022	790	6812	25.7	
Controls*	5122 ±438(4)	3068 ±294(4)	8190 ±511(4)	100.0	29913±3457(3)

* Control values were obtained from autopsy material, and expressed as mean±SD for the number of cases indicated in brackets

Neurons in the intermediolateral columns, Clarke's columns, Onufrowicz nuclei, and other spinal cord structures

Neurons in the intermediolateral columns in the thoracolumbar segments and in Onufrowicz nuclei in the sacral segments were well preserved in all 3 autopsied cases. Neurons in Clarke's columns were also well populated. There was no apparent degeneration in the pyramidal tracts. Myelinated fibres in the long tracts of the spinal cord other than the fasciculus gracilis was well preserved.

Neurons in the brainstem and central nervous system (CNS)

Neurons in the hypoglossal, facial and trigeminal motor nuclei were severely depleted or atrophic, while those in the trochlear, abducens and oculomotor nuclei were well populated. Myelinated fibre populations and fibre size distributions of the trochlear, abducens and oculomotor nerve roots examined in one case were not different from control values (Table 3). Neurons in the gracile and cuneate nuclei were well populated. The CNS was otherwise normal by light microscopy.

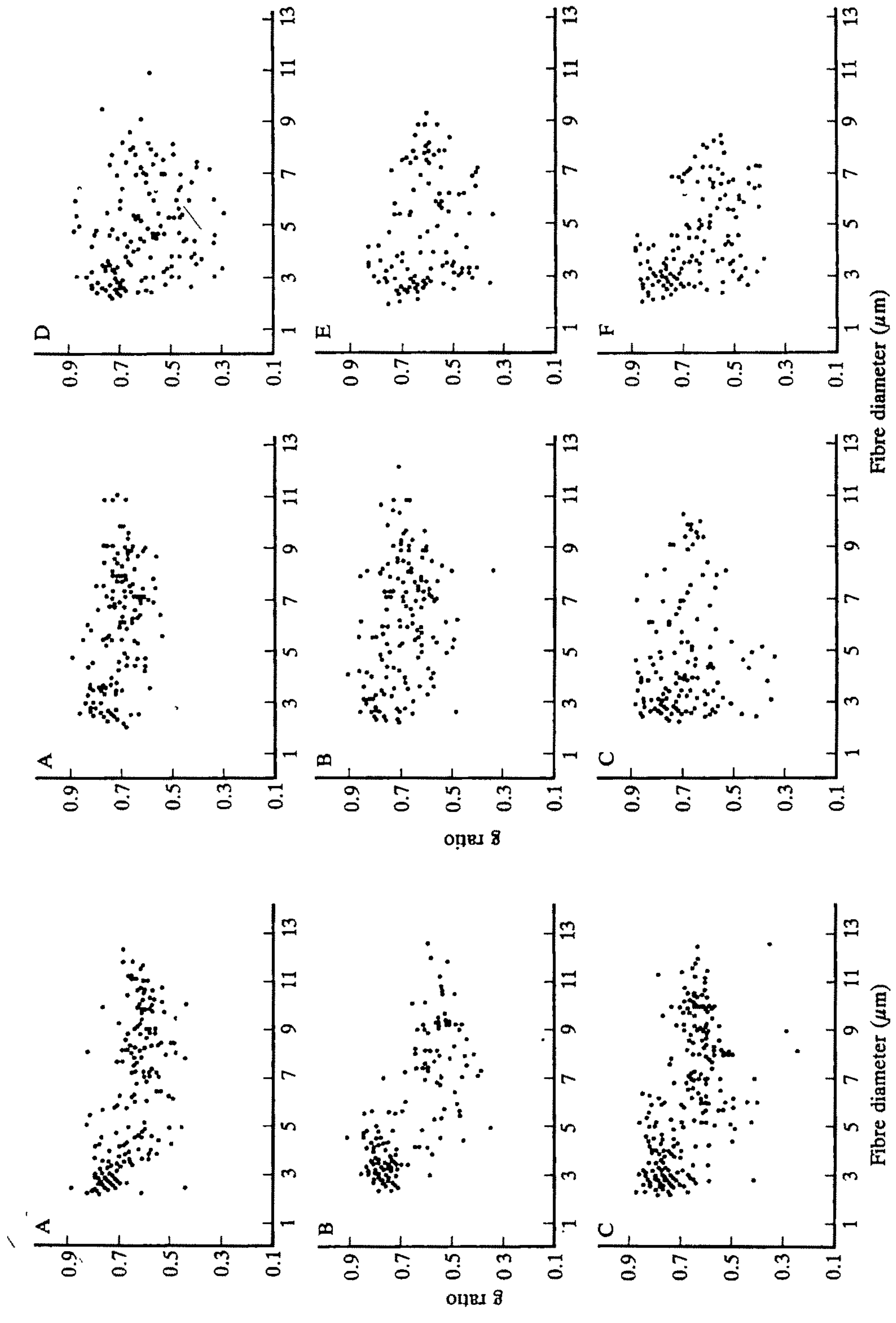

FIG 7. Scattergrams showing relationship of g ratio to fibre diameter. Left hand panel shows those from the sciatic nerves (A, *control*; B, *Case 1*; C, *Case 2*). Right hand panels shows those from the sural nerves (A, *control*; B, *control*; C, *Case 2*; D, *Case 4*; E, *Case 5*; F, *Case 6*).

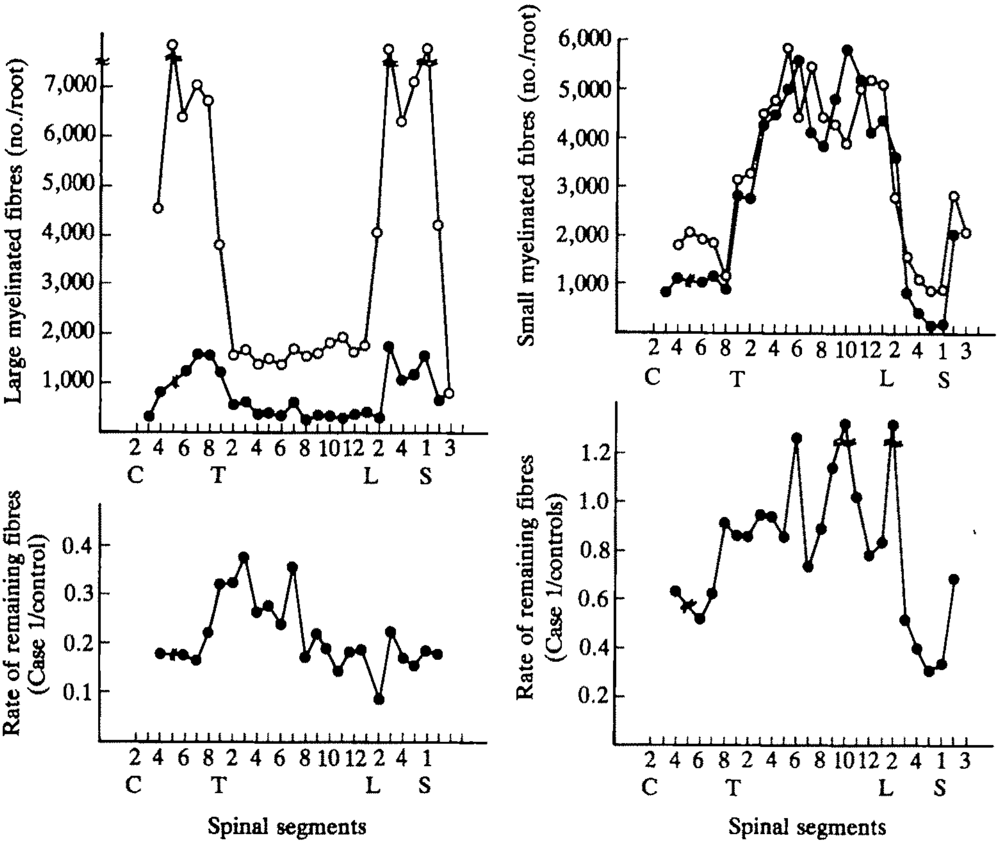

FIG. 8. Rostro caudal distribution of large (≥ 6.73 μm) and small (< 6.73 μm) myelinated fibres in the ventral spinal roots in terms of spinal segments Open circles indicate the mean of 3 controls. Closed circles are the values for *Case 1*. C = cervical, T = thoracic; L = lumbar; S = sacral.

Muscles

Hypertrophic fibres, often containing internal nuclei, fibre splitting, groups of atrophic fibres and clumping of sarcolemmal nuclei were common findings in all samples. Muscle fibres were frequently replaced by adipose tissue. Histochemical staining (ATPase) showed fibre type grouping with large groups of type 1 and type 2a fibres.

DISCUSSION

The clinical, genetic and electrophysiological features of our cases are similar to those previously described for X-linked recessive bulbospinal neuronopathy. Sensory impairment and corresponding low or absent sensory action potentials are in agreement with the observations by Harding *et al.* (1982) and Wilde *et al.* (1987), which indicates that the involvement in this disease is not restricted to motor efferents but that the sensory system is also universally involved. Neuronal cell bodies in the dorsal root ganglia and fibres in dorsal spinal roots were fairly well preserved in population and morphology. Myelinated axons in the fasciculus gracilis, sciatic, tibial and sural nerves showed a distally accentuated axonal loss without prominent active degeneration. Segmental demyelination and remyelination, significantly clustered on individual fibres, and an increased variability in g ratios in the sural nerve in some cases suggests that the segmental demyelination observed in this disease may be secondary to axonal damage (Dyck and Lais, 1973; Dyck *et al.*, 1981). These observations also suggest that a distal axonopathy resulting from perikaryal dysfunction in the primary sensory neurons is part of the underlying pathological process.

The highly selective involvement of fibres in the fasciculus gracilis in the autopsied cases, and predominant lower leg involvement in clinical sensory impairment suggests that involvement in primary sensory neurons is caudally dominant in terms of rostrocaudal segmental distributions (Collier and Buzzard, 1903; Foerster, 1936; Smith and Deacon, 1984).

In contrast to the primary sensory neurons, motor neurons were lost throughout all the spinal segments and in some lower brainstem motor nuclei innervating facial and bulbar musculature. The magnitude of motoneuron loss was more extensive than that for primary sensory neurons. Although distally accentuated axonal loss in motoneurons was not clearly documented in this study, the absence of central chromatolysis combined with the presence of simple atrophy suggests the loss of motor neurons is not a retrograde phenomenon but a primary neuronal perikaryal event. Despite a distal predominance in sensory impairment in the lower limbs, muscle wasting was greater in proximal limb muscles. The rostrocaudal distributions of the pathological involvement in motor and sensory neurons was proportional to the clinical manifestations, but the pathological basis for the proximodistal gradient of muscle wasting in the limbs is not clear.

In both lower motor and primary sensory axons, axonal sprouting with the formation of regeneration clusters was rarely observed, but the widespread presence of motor unit potentials of increased amplitude and of fibre type grouping on muscle biopsy indicates that collateral reinnervation occurs at the periphery. In chronic genetic disorders where there is axonal loss in peripheral nerves such as in type II hereditary motor and sensory neuropathy (Berciano *et al.*, 1986) and neuroacanthocytosis (Sobue *et al.*, 1986*a*), sprouting of the proximal portions of the axons commonly follows distal degeneration. The rare occurrence of proximal regenerative activity in X-linked recessive bulbospinal neuronopathy may be the reflection of genetically determined inability of the neurons to regenerate in this condition.

When we compared the pathological characteristics of lower motor and primary sensory neurons, they differed in the severity of neuronal loss, in the rostrocaudal distribution of involvement and possibly in the distally accentuated pattern of axonal loss. The low incidence of proximal axonal sprouting was common to both sensory and motor axons. Although the process of gene expression resulting in neuronal loss in not known, the phenotypic expression of the same pathological factor could differ between the lower motor and primary sensory neurons.

Five reports on the postmortem findings in X-linked recessive bulbospinal neuronopathy have been published (Magee, 1960; Kennedy *et al.*, 1968; Paulson *et al.*, 1980; Mukai *et al.*, 1981; Sobue *et al.*, 1981*a*, *b*; Nagashima *et al.*, 1987). Loss of myelinated fibres in the fasciculus gracilis, neuronal loss in the ventral horns throughout all spinal segments with loss of myelinated fibres in the ventral spinal roots, preservation of Clarke's column nuclei and intermediolateral column nuclei and myelinated fibres in the long tracts of the spinal cord other than the fasciculus gracilis are common to all previous reports and to our 3 postmortem cases. The pyramidal tract has also been considered to be well preserved, as was true for the present cases. The reported findings varied little in the distribution and magnitude of the neuronal loss between the individual cases, which may correspond to the limited variation in the clinical manifestations between cases.

Distally accentuated axonal loss with a low incidence of active degeneration that presumably reflects a slowly progressive neuronal degeneration, and the predominant involvement of the sacral and lumbar primary sensory neurons has been well documented both in type I and II hereditary motor and sensory neuropathy (Hughes and Brownell, 1972; Smith *et al.*, 1980; Dupuis *et al.*, 1983; Dyck, 1984; Dyck *et al.*, 1984; Berciano *et al.*, 1986) and Friedreich's ataxia (Dyck and Lais, 1973; Said *et al.*, 1986). For X-linked bulbospinal neuronopathy, however, the pathology in primary sensory neurons was less severe and lower motor neuron involvement was more marked as compared with these diseases. The mode of distribution of lower motor neuron involvement, with preservation of neurons innervating external ocular muscles despite the fact that other brainstem motor neurons are universally affected, motor neuron loss in the ventral spinal horns throughout all spinal segments, and preservation of Onufrowicz nuclei in the sacral spinal cord (Mannen *et al.*, 1977) are similar to those observed in amyotrophic lateral sclerosis (ALS) (Mannen *et al.*, 1977; Kawamura *et al.*, 1981; Sobue *et al.*, 1981*a*, *b*) or Werdnig-Hoffmann disease (Iwata and Hirano, 1978*a*, *b*). Moreover, primary sensory afferents have been shown to be involved to some extent in clinically 'pure' motor neuron diseases such as hereditary ALS (Engel *et al.*, 1959; Hirano *et al.*, 1967), sporadic ALS (Mulder *et al.*, 1983; Brock and McIlwain, 1984; Jamal *et al.*, 1985) and Werdnig-Hoffmann disease (Marshall and Duchen, 1975; Brock and McIlwain, 1984), although the precise nature of the pathology in the primary sensory neurons has not been well characterized.

Recently, the gene locus for X-linked bulbospinal neuronopathy was identified in the vicinity of the locus DXYS1 in the proximal long arm of the X chromosome. The DXYS1 locus was also linked to that of X-linked hereditary motor and sensory neuropathy (Fischbeck *et al.*, 1986*b*). X-linked bulbospinal neuronopathy and X-linked hereditary motor and sensory neuropathy differ in their clinical manifestations (Fischbeck *et al.*, 1986*a*), but some of the pathological processes could be common between these two disorders. Similarities in the pathological characteristics of the primary motor and sensory neuron involvement between X-linked bulbospinal neuronopathy and other hereditary neuropathies suggest that some hereditary motor and sensory neuronopathies may share a common pathway in the process of neuronal loss. Studies to clarify the precise pathological nature of lower motor and primary sensory neuron involvement in hereditary motor and sensory neuronopathies should be continued to identify the mode of phenotypic expression of the abnormal genes.

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THE BEREITSCHAFTSPOTENTIAL IS ABNORMAL IN PARKINSON'S DISEASE

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SUMMARY

The average Bereitschaftspotential (BP) preceding a rapid, self-paced voluntary extension movement of the index finger was recorded from 6 scalp locations in 14 patients with Parkinson's disease who had been withdrawn from their normal drug therapy for at least 12 h before testing. The amplitude of the potential was measured at the peak negativity (N1) and 650 ms prior to this (NS1), and compared with that recorded in a group of 12 age-matched control subjects. The N1 amplitude was the same as in the normals, but the NS1 component was smaller in the patients, especially in midline leads. As a result, the rise in the BP between the peak NS1 and N1 component (termed NS2) was larger in the patient group.

The NS1 component of the BP is thought to reflect preparatory activity in the supplementary motor area (SMA) of cortex. Since the basal ganglia provide a major source of afferent input to SMA, the reduction in NS1 in the patients probably results from inadequate basal ganglia activation of SMA. The larger NS2 component may reflect extra activity in other brain areas to compensate for the reduced SMA activity.

INTRODUCTION

Several lines of evidence emphasize the role of the supplementary motor area (SMA) in the breakdown of motor control in Parkinson's disease. Anatomical studies of primate basal ganglia systems show that a major portion of pallidal output is directed to the nonprimary motor areas of frontal cortex, in particular to the SMA (Jürgens, 1984; Schell and Strick, 1984). In man, preliminary reports have suggested that the SMA is crucial to the organization of sequential hand movements (Roland *et al.*, 1980, 1982) and an abnormality of sequencing hand and elbow movements has been demonstrated in a patient with unilateral SMA damage (Dick *et al.*, 1986). A similar disturbance of sequenced hand and elbow movements has been demonstrated in patients with Parkinson's disease (Benecke *et al.*, 1987).

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Deecke and Kornhuber (1978) suggested that the activity of the SMA may be studied by averaging surface electroencephalographic (EEG) activity during the organization and performance of a self-paced voluntary movement. Such a movement is usually preceded by an EEG potential termed the Bereitschaftspotential (BP) after Kornhuber and Deecke (1965). Deecke and Kornhuber (1978) and Deecke (1985) argued that the BP may reflect activity in the SMA, as its maximum amplitude is at the vertex (overlying the SMA) for several different types of voluntary movement (eye, hand, arm and foot). In a recent review, Tamas and Shibasaki (1985) divided the BP into an early and a late component. The late component is lateralized to the hemisphere contralateral to the limb movement and is thought to represent activity in the motor cortex (Shibasaki *et al.*, 1978). The early component is not lateralized and reaches its maximum amplitude over the midline. Boschert *et al.* (1983), Boschert and Deecke (1986) also concluded that it is the early BP, rather than the late component, which reflects SMA activity, as specific late lateralized components can be distinguished for hand and foot movements.

As the main functional target area for pallidal output is the SMA, an abnormality of the BP would be anticipated in Parkinson's disease, and this might selectively affect the early BP. Initial BP studies from different laboratories suggested that there was an abnormally small BP in Parkinson's disease (Deecke *et al.*, 1977; Shibasaki *et al.*, 1978). Recently, however, certain methodological difficulties in this earlier work have been reassessed (Barrett *et al.*, 1985*a*, 1986*a*); it has been suggested that the apparently smaller BP observed in Parkinson's disease could have arisen as a result of problems in triggering the averager due to the gradual onset of EMG activity in akinetic patients (Barrett *et al.*, 1986*b*). In addition, it has become clear that the amplitude of the BP is critically dependent on age. Barrett *et al.* (1985*b*) and Deecke (1985) have found that older normal subjects have a smaller BP than younger control subjects, and that the use of younger control subjects therefore may have skewed the statistical results. With improved triggering and the use of older normal subjects for comparison, Barrett *et al.* (1986*b*) suggested that no difference exists between the BP of normal old subjects and patients with Parkinson's disease.

Treatment of patients with Parkinson's disease may also confound BP studies. In a previous paper (Dick *et al.*, 1987) we pointed out that the oral administration of levodopa altered the amplitude of the BP, particularly of the early BP, in both patients with Parkinson's disease and normal subjects. Some of the patients studied by Barrett *et al.* (1986*b*) were on drug therapy when they were investigated. This would have caused an increase in the early BP component which could have hidden any decrease in its size. When drug administration was withheld for at least 18 h we found, like Barrett *et al.* (1986*b*), that the peak BP negativity of patients with Parkinson's disease was normal for simple finger extension movements; however, unlike Barrett *et al.* (1986*b*), we found a suggestion that there was a smaller early component of the BP in the patients with Parkinson's disease.

There also was a tendency to a small increase in the late lateralized component, but this did not reach statistical significance in the small number of subjects studied in this earlier investigation.

Whether there really is a difference between the BP of patients with Parkinson's disease and control subjects remains uncertain. In this paper we report the results of BPs collected from 14 parkinsonian subjects and from 12 age-matched control subjects. All the patients had been withdrawn from antiparkinsonian medication overnight and all were profoundly parkinsonian when examined.

SUBJECTS AND METHODS

Fourteen right-handed patients with Parkinson's disease aged 59.0 ± 10 yrs (mean ± SD) (range 29–77 yrs) gave informed consent to be studied; they all had longstanding disease and were regular attenders at a specialist Parkinson's disease clinic. They were studied at least 12 h after their last dose of antiparkinsonian medication at a time when profoundly parkinsonian. Their clinical features are summarized in the Table. Their results were compared with those from 12 right-handed control subjects who also gave informed consent to be studied; their mean age was 58.7 ± 12 yrs (mean ± SD) (range 40–82 yrs). Four were elderly relatives of the authors, 4 were older colleagues in the laboratory, 3 were spouses of patients and 1 subject had bilateral carpal tunnel syndrome.

Details of the method for recording and averaging the BP are described in a previous paper (Dick

TABLE PATIENTS STUDIED

Case	*Age (yrs)*	*Sex*	*Disease duration (yrs)*	*Therapy*[a]	*Akinesia*[b]	*Rigidity*[b]	*Tremor*[b]	*Hoehn/Yahr*[c] *grade*
1	60	M	14	Benzhexol* S 250 2 hrly	+++	+++	+	IV
2	56	M	8	Benzhexol S 250 3 hrly	+++	+	++	IV
3	65	F	29	Benzhexol L-DOPA 1 g 5 hrly	+++	++	O	IV
4	54	M	19	S 250 2 hrly	+++	+++	+	IV
5	58	M	8	Benzhexol	++	++	O	III
6	61*	M	5	S 125 4 hrly	++	++	++	III
7	56*	M	7	S 100 2 hrly**	+++	+	O	III
8	29	M	12	S 100 2 hrly	++	++	++	III
9	70	F	8	S 100 3 hrly	++	++	O	III
10	50	M	6	S 100 2 hrly	++	++	O	III
11	68	M	12	S 50 2 hrly	++	++	O	III
12	65	M	5	S 125 3 hrly	++	++	O	III
13	58	M	9	S 125 5 hrly	++	+	O	II
14	76	M	12	S 125 5 hrly	++	+	O	II

[a] S = Sinemet (L-DOPA plus carbidopa); dose of levodopa and frequency are shown. ** Other dopaminergic agonists also taken, e.g., bromocriptine or pergolide. [b] Parkinsonian symptoms were rated clinically: O = absent, + = mild, ++ = moderate, +++ = severe. [c] Hoehn and Yahr grading: I, unilateral parkinsonism, II, bilateral parkinsonism, intact balance; III, mild disability, impaired righting reflexes; IV, moderate disability, frequent falls; V, bedbound. * Left hand tested due to excess tremor or minimal hypokinesia in right hand.

et al., 1987). Briefly, EEG potentials preceding self-paced index finger extension were averaged on-line from 128 movements by a Digitimer D200 computer from 6 scalp electrode positions (C3, C4, Cz, 4 cm anterior to Cz, called here FCz; 3 cm anterior to C3, here called C3A; and 3 cm posterior to C3, here called C3P). Bandpass filters were set 3 dB down at 0.03 and 300 Hz. In all control subjects and in all but 2 of the patients (*see* Table), the dominant (right) hand was tested.

Subjects were instructed to fixate on an object directly in front of them and not to blink during finger movements. Movements were small rapid finger flicks made in the subjects' own time and not initiated in response to any cue, either external (e.g., sound or peripheral vision) or internal (e.g., mental counting or respiration). Although the patients moved 10–20% more slowly than normal, we have reported previously (Dick *et al.*, 1987) that this makes little difference to the BP in normal subjects. The D200 computer could not accept EEG activity sooner than 5 s after the previous movement. The usual intermovement interval lay in the range 6–15 s, which is similar to those used in other studies (4–12 s, Boschert and Deecke, 1986; greater than 3 s, Barrett *et al.*, 1986*a*, *b*; 5–10 s, Shibasaki *et al.*, 1978).

Scalp muscle activity and blink artefacts were excluded by a sensitive reject facility which automatically rejected any potential greater than ±0.1 mV. Eye movements were not monitored separately by electro-oculography since the FCz electrode reliably registered vertical eye movements which tended to be greater than 0.3 mV (peak-to-peak). Appropriate rejection could be confirmed by the experimenter who constantly monitored ongoing EEG activity. Digitized EEG data were collected in 12 patients and all controls for 2.9 s before, and 1.2 s after the upstroke of the EMG recorded from surface electrodes placed over extensor indicis (in the first 2 patients studied, data were recorded for 1280 ms before and 1280 ms after the onset of EMG). It was normalized at each of the 6 electrode positions by drawing a horizontal regression line (calculated by computer) through the first 32 digital points of each record. This horizontal line was used as a zero and the amplitudes of the BP were measured using a 10 μV calibration signal BP amplitude was measured at (1) peak BP negativity (N1) (a clearly defined N1 was visible in one of the 6 scalp leads in all subjects, and the amplitude measurements of the other leads were made at this time), and (2) 650 ms before EMG onset, which marks the transition from the early to the late component of the BP (Tamas and Shibasaki, 1985); the amplitude of the BP 650 ms before EMG onset thus represents the size of the early component of the BP (NS1). The late lateralized component of the BP (NS^1 of Tamas and Shibasaki, 1985; here referred to as the NS2) was calculated by subtracting the NS1 from the peak BP negativity (N1). Measurements of NS1 were made at a constant time, rather than at the point where the slope of the two premovement potentials changed since we found that it was not always possible to determine the latter reliably by eye; nor could we determine the exact time of onset of the BP in all subjects.

The BPs from all scalp electrode positions both in patients with Parkinson's disease and age-matched control subjects were compared by an analysis of variance for repeated measures (ANOVA) with a grouping factor of patients/normals and a within-subject factor of electrode position. Data from the C4 electrode position were included in the analysis of the early component of the BP (NS1) as this component has a symmetric distribution over both hemispheres, but it was not included in the analysis of the N1 and the NS2 components as they were lateralized. The significance, or not, of the F value was assessed using the conservative correction of Greenhouse and Geisser (1959) which is designed to avoid nonreplicable positive results by restricting the theoretically appropriate degrees of freedom. BP amplitudes from specific electrode positions were compared between groups using Student's t test.

RESULTS

Bereitschaftspotentials recorded from 6 scalp locations, together with the triggering EMG potential, are shown for a single normal subject and a typical

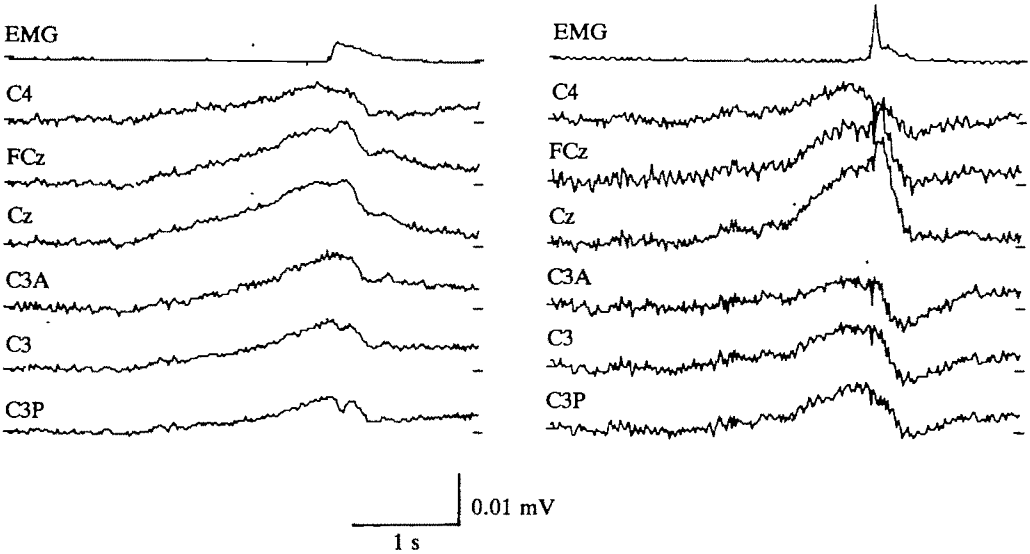

FIG. 1. BPs recorded from 6 EEG leads (*bottom 6 traces*) and rectified EMG from extensor indicis muscle (*top trace*) from a normal subject (*left*) and a typical patient with Parkinson's disease (*right*) Sweeps are the average of 128 self-paced finger extension movements with collection triggered by the onset of EMG activity Vertical dotted lines are at time of EMG onset and 650 ms beforehand Scalp locations of the EEG electrodes are shown in the diagram of fig 2, linked earlobes served as the reference The early slowly rising slope of the BP (to −650 ms) is much less prominent in the patient than in the normal subject, even though the peak BP is of approximately similar size (or even larger at Cz)

patient with Parkinson's disease in fig. 1. Averaged BP traces from all the normal subjects are superimposed with those from 12 of the patients with Parkinson's disease in fig. 2 (the data from 2 of the patients with Parkinson's disease were not included as their BPs had been collected using a different time scale). The averaged sizes for each BP component (N1, NS1 and NS2) in the normal subjects is contrasted with those from all the patients with Parkinson's disease for each electrode position in fig. 3.

There was no significant difference in the amplitude of the BP at N1 between patients and controls for any individual electrode position (F = 0.03, df 1,24, $P > 0.05$, fig. 3). The ANOVA comparison demonstrated that the N1 amplitude had a similar distribution over the contralateral hemisphere for the two groups; this was manifest statistically as a significant effect of 'electrode position' (F = 28.53, df 4,96, $P < 0.01$) in the absence of a significant interaction between the grouping and the within-subject factors (F = 1.49, df 4,96, $P > 0.05$).

The amplitude of the early component of the BP (NS1) was smaller than normal in patients with Parkinson's disease (F = 14.4, df 1,24, $P < 0.01$). For the NS1 there was a significant effect of 'electrode position' (F = 24.26, df 5,120, $P < 0.01$)

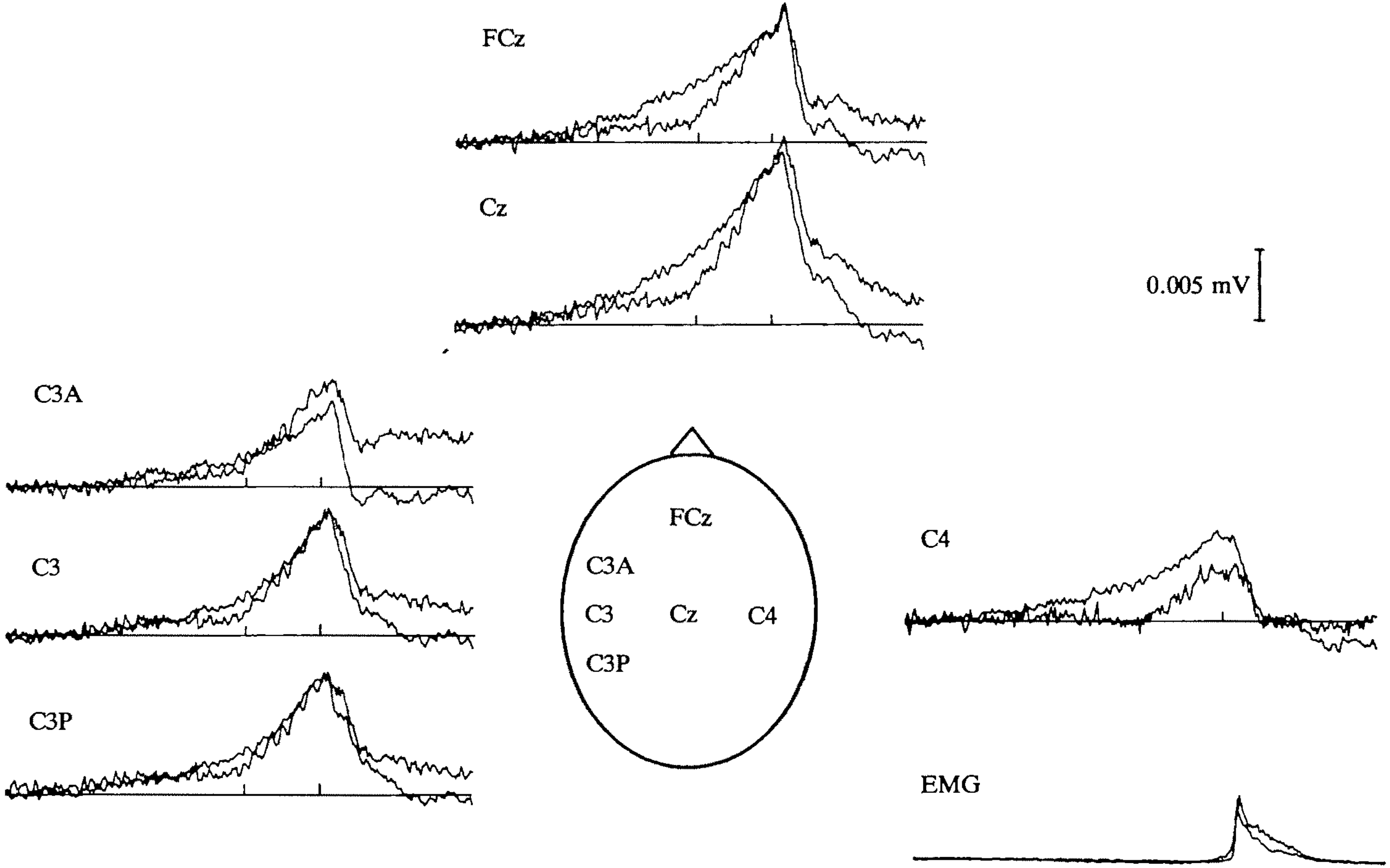

FIG. 2. Averaged BPs in 12 patients with Parkinson's disease are superimposed on those from 12 age-matched normal subjects. Averaged extensor indicis EMG is shown in the *bottom right*, and are similar in patients and controls. Markers on the time base (3.1 s) are shown at time zero (EMG onset) and at 650 ms before EMG onset. For the early part of the BP the smaller amplitude traces belong to the patients with Parkinson's disease: following finger movement the traces cross in all leads except C3A where they cross before finger movement, this gives a consistently smaller postmovement positivity in the patients' traces. For the patients, the NS2 is significantly larger at FCz ($P < 0.05$) and C3A ($P < 0.05$) and the NS1 is significantly smaller at C4 ($P < 0.01$), Cz ($P < 0.05$) and FCz ($P < 0.02$)

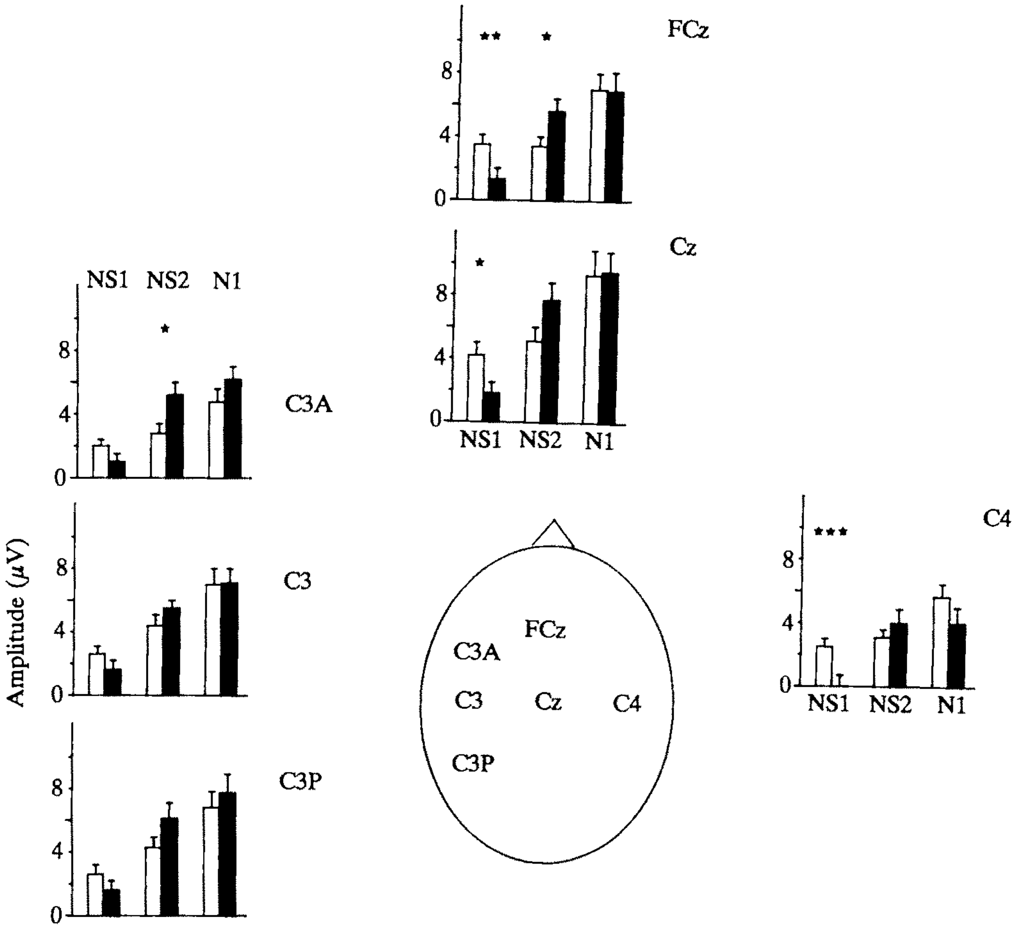

FIG 3. Averaged results for the NS1, NS2 and N1 components of the BP in 12 age-matched normal subjects (open bars) and 14 patients with Parkinson's disease (hatched bars) at 6 electrode positions Mean and SEMs are shown P values (Student's t test) are shown. * $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$

and a significant interaction of 'group' and 'electrode position' (F = 8.9, df 5,120, $P < 0.025$). Although the NS1 was larger in the control subjects in all leads, the distribution of that change was different. Fig. 2 shows that the decrease of NS1 in patients with Parkinson's disease was more marked over the midline and over the ipsilateral hemisphere than over the contralateral hemisphere. This observation is more clearly illustrated in fig. 3 which shows that the decrease in the NS1 in the patients with Parkinson's disease was significantly greater over the ipsilateral motor cortex at C4 ($P < 0.01$) and over the midline both at FCz ($P < 0.02$) and at Cz ($P < 0.05$); however, it did not reach statistical significance at any individual lead over the contralateral motor cortex (C3A, C3, C3P).

The decreased amplitude of the early BP (NS1) was offset by a larger than normal late BP or NS2 in patients with Parkinson's disease (F = 9.9, df 1,24,

$P < 0.01$). Here the ANOVA comparison showed an effect of 'electrode position' ($F = 23.34$, df 4,96; $P < 0.01$), but the interaction term failed to reach statistical significance after the conservative correction of Greenhouse and Geisser was applied ($F = 2.48$, df 4,96; $P > 0.05$). Fig. 3 suggests that the NS2 may have been larger in the patients with Parkinson's disease over the contralateral hemisphere anteriorly (C3A: $P < 0.05$) and over the midline anteriorly (FCz: $P < 0.05$).

DISCUSSION

One of the main findings from this study was that the early phase of the BP was smaller than normal in patients with Parkinson's disease. This difference was more prominent over the midline and over the ipsilateral motor cortex than it was over the motor cortex contralateral to the finger moved. The other major finding was that, in contrast to this poor early development of BP negativity, the patients with Parkinson's disease developed a larger than normal late phase of the BP (the NS2 component), at least in the anterior midline and contralateral leads. Thus our results confirm those of Barrett *et al.* (1986*b*) in showing that peak BP is normal in Parkinson's disease. This is apparently at odds with the reports of Deecke *et al.* (1977) and Shibasaki *et al.* (1978) that there is a decrease in the peak BP in patients with Parkinson's disease. As pointed out in the Introduction, methodological problems in this early work may account for this discrepancy.

The finding that the NS1 is reduced in Parkinson's disease is new. Measurements of the BP were not made at this timing in the early studies. Barrett *et al.* (1986*b*) measured at this point but found no difference between patients and normals. However, some of their patients were studied on drug treatment. We have shown previously (Dick *et al.*, 1987) that administration of L-DOPA can increase the amplitude of the BP and, as already stated, this may account for the difference between the two sets of results. More recently, Simpson and Khuraibet (1987) have shown a delay in onset of the BP in patients with Parkinson's disease. Although we did not measure latency in the present experiments, it may well be that a smaller NS1 would lead to such a result because of difficulties in defining its onset.

The decreased amplitude of the early BP from midline leads in patients with Parkinson's disease may be due to impaired SMA function. This would be consistent with the hypothesis that SMA function is abnormal in Parkinson's disease (Benecke *et al.*, 1986, 1987). However, there is as yet no definitive proof that the early component of the BP arises in SMA. It is also not entirely clear why there is such an obvious change in the early BP over the ipsilateral motor cortex. This may be a reflection of both the unusual callosal connectivity of the hand areas of the motor cortex (Pandya and Vignolo, 1971), or of the intimate role played by the SMA in the control of bilateral hand movements (Brinkman, 1984; Roland *et al.*, 1980, 1982). It is known that coordinated interplay of the two hand motor cortices is heavily dependent on SMA function in the monkey (Brinkman, 1984), and that there are no direct callosal connections between the two hand motor cortices (Pandya and Vignolo, 1971). It may be that, as a result of SMA dysfunction, patients with Parkinson's disease have particularly poor communication between the two hand motor cortices during hand movements.

With regard to the later lateralized components of the BP, Shibasaki *et al.* (1978) have suggested that the dentatothalamic tract and motor cortex are involved in their generation, and this is supported by animal studies (Sasaki *et al.*, 1981, 1985). Our results in Parkinson's disease show a more prominent negativity than normal in this late phase of the BP. It is possible that this observation represents the superimposition of a second type of slow electronegative brain potential in patients with Parkinson's disease, known as the CNV. This potential, first described by Walter *et al.* (1964), occurs before a movement that is triggered by an imperative stimulus (IS). The subject is warned of the impending arrival of the 'IS' by a warning signal, usually 2 s or so beforehand. The amplitude of the CNV probably reflects the subject's state of arousal as it is decreased after sleep deprivation (Irwin *et al.*, 1966) and may be altered in anxiety states (Sartory, 1985). It is also smaller in patients with Parkinson's disease when off treatment than when on treatment (Amabile *et al.*, 1986). If the patients linked their motor performance more closely than normal subjects to an environmental cue, such as the preceding finger movement, elements of a CNV might be expected to emerge. However, in their comparative study of the CNV and the BP, Grünewald *et al.* (1979) showed a specific distribution for each potential; the CNV was not lateralized and the larger amplitude, late negativity of the CNV, was posterior. The distribution of the NS2, by contrast, was anterior and lateralized. This suggests that the NS2 is generated by different mechanisms from those involved in the generation of the CNV.

What then does the defective early BP and the prominent later negativity reflect in terms of the breakdown of movement control in Parkinson's disease? Goldberg (1985) has suggested that there are two distinct systems for the control of voluntary movements. The first is a predictive feedforward mode whereby the subject decides 'internally' the format of a desired movement. The second is a responsive mode whereby the subject responds to environmental cues which themselves determine how a motor response is organized. On the basis of embryological, anatomical and neurophysiological evidence (primate lesion studies, cortical single unit studies and blood flow studies), Goldberg (1985) suggests these two systems are anatomically distinct; the former involves the medially-situated SMA, the latter involves the dorsolateral premotor area. Connectivity studies in primates suggest that the major input to SMA is ultimately derived from the basal ganglia (Jürgens, 1984; Schell and Strick, 1984), whereas the dorsolateral PMA has a significantly greater input from areas of sensory cortex, particularly the visual cortex (Pandya and Kuypers, 1969). It is tempting to suggest that patients with Parkinson's disease rely on the dorsolateral system of motor control as their medial system is defective. This would be consistent with the inordinate dependence of parkinsonian patients on visual information for successful initiation and performance of a variety of movements. In some patients, the rhythm and onset of walking can be improved by painting parallel lines on the ground (Martin, 1967), and the performance of a manual tracking task by parkinsonian patients declines abruptly if segments of visual information are removed (Flowers, 1976, 1978; Stern *et al.*, 1983).

This model of SMA and premotor area function permits an interpretation of our BP findings. The impaired early BP may reflect poor cortical activation of the medial predictive system involving SMA and basal ganglia. The augmented negativity in the late phase of the BP, which is probably most marked dorsolaterally, may reflect compensatory overactivity of the lateral 'responsive' system involving the dorsolateral PMA and visual (and other) sensory systems.

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CYTOMEGALOVIRUS IN THE NERVOUS SYSTEM OF PATIENTS WITH THE ACQUIRED IMMUNE DEFICIENCY SYNDROME

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SUMMARY

Clinicopathological features of infection of the nervous system by cytomegalovirus (CMV) in 31 patients with the acquired immune deficiency syndrome (AIDS) are reviewed. Neuropathology was variable, ranging from rare isolated CMV inclusions in brain without associated inflammation or necrosis, to severe necrotizing ependymitis and meningoencephalitis. In 1 patient, CMV had produced a necrotizing meningoradiculitis which presented clinically as ascending paralysis. In the brains and spinal cords of 6 patients, evidence of human immunodeficiency virus (HIV) infection of neural parenchyma was seen in close proximity to CMV infection. Both viruses individually or together were associated with low grade (microglial nodule) encephalitis. In retrospect, the diagnosis of CMV had been a difficult one to make clinically in neurologically impaired patients with AIDS. The results suggest that CMV may also localize in the nervous system without significant clinical sequelae. Imaging studies and analysis of cerebrospinal fluid revealed abnormalities in many patients, but none of them (short of culture of CMV itself in two cases) appeared to be specific to this neurological complication of the immunodeficiency.

INTRODUCTION

Neurological and neuropathological complications of systemic infection with the human immunodeficiency virus (HIV), specifically acquired immune deficiency syndrome (AIDS), encompass various opportunistic infections, cerebral lymphoma, vascular lesions and miscellaneous abnormalities including those of white matter (Snider *et al.*, 1983; Levy *et al.*, 1985; Anders *et al.*, 1986*a*, *b*; Fenelon *et al.*, 1986; Petito *et al.*, 1986; Rosemberg *et al.*, 1986; Fischer and Enzensberger,

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1987). Direct HIV infection of the central nervous system (CNS) is well documented (Shaw *et al.*, 1985; Stoler *et al.*, 1986; Wiley *et al.*, 1986*a*; Vazeux *et al.*, 1987), and strains of HIV that show tropism for specific cell populations within brain have been isolated (Koyanagi *et al.*, 1987). A common opportunistic pathogen producing neuropathology in patients with AIDS is cytomegalovirus (CMV) (Anders *et al.*, 1986*a*, *b*; Petito *et al.*, 1986). Its heterogeneous effects were initially recognized in the central neuraxis, but sequelae of CMV infection in the peripheral nervous system (PNS) are now appreciated (Bishopric *et al.*, 1985; Eidelberg *et al.*, 1986; Behar *et al.*, 1987).

The purpose of this report is to review the neuropathology in cases of CMV affecting the nervous system of AIDS patients. Several issues relevant to CMV infection of neural tissues in these severely immunocompromized individuals will be emphasized, namely (1) the full neuropathological spectrum of CMV infection, cell types involved, etc.; (2) coinfection of brain by CMV and HIV as well as other neuropathology and systemic pathology seen concomitantly with CMV infection of brain; (3) the relationship between CMV and microglial nodules (MGNs) commonly observed in brains of patients with AIDS; and (4) clinicopathological correlation. The working hypotheses that formed the basis for this study, based on preliminary observations, were (1) that CMV can induce heterogeneous structural abnormalities associated with variable degrees of tissue response in the nervous system, and (2) that CMV infection might be found with characteristic patterns of neuropathology in AIDS patients, such as associated opportunistic infections, tumours and HIV infection of brain.

MATERIALS AND METHODS

Source and processing of tissues

The criterion for inclusion of an AIDS patient in this review was the finding of CMV infection, using conventional light microscopic histological criteria (Anders *et al.*, 1986*a*, *b*; Morgello *et al.*, 1987), in the CNS and/or PNS at necropsy. Over 160 patients with the clinical syndrome of AIDS (the large majority) or AIDS-related complex (ARC), have been examined at autopsy at the UCLA Center for the Health Sciences and the Wadsworth Veterans Administration Hospital since 1981 (Anders *et al.*, 1986*a*, *b*; Vinters *et al.*, 1989). Almost all patients have been male, and 75–80% have had homosexuality or bisexuality as the major risk factor for AIDS. This study included tissues from 2 patients initially examined at postmortem in Montreal and Newport Beach, California. Although diagnostic criteria and methodologies used to establish the clinical diagnosis of AIDS have changed over the time during which the tissues were removed, the autopsy examination of organs, particularly the brain, spinal cord and peripheral nerve, has been performed in a systematic way (Anders *et al.*, 1986*b*). Tissues have routinely been fixed in 10% neutral buffered formalin for 10–14 days before sectioning, and blocks of grossly visible lesions and normal appearing brain have been sampled for histological assessment. More recently, virtually all brains taken from patients with the diagnosis of AIDS or ARC have been sampled using a systematic blocking diagram that ensures extensive and consistent (from case to case) examination of large regions of cortex, subcortical white matter, deep grey matter, brainstem, cerebellum and spinal cord. This protocol generates 23 tissue blocks (2 5 × 2.5 cm in size), which are taken in addition to those of grossly identifiable brain or spinal cord lesions Tissues sampled according to this protocol were available for examination in 11 of the 31 patients, and were studied to assess colocalization of CMV, MGNs and HIV-associated multinucleate giant cells within regions of brain. All blocks were routinely stained with haematoxylin and eosin, and special stains (e.g., Weil, Kluver-Barrera, Bielschowsky) have been performed as necessary to demonstrate abnormalities of myelin, axons, etc. An immunocytochemical procedure (peroxidase antiperoxidase) for glial fibrillary acidic protein (GFAP) has been used to demonstrate astrocytic gliosis (Eng and DeArmond, 1982). Electron microscopy has been carried out on tissues originally fixed in either buffered glutaraldehyde or formalin as described above, using established techniques (Hunter, 1984).

In situ hybridization

In selected cases, in situ hybridization to localize CMV or herpes simplex virus (HSV) DNA in paraffin sections has been performed as follows (Brigati *et al.*, 1983; Unger *et al.*, 1986; Grody *et al.*, 1987). Sections were deparaffinized in xylene, dehydrated through graded concentrations of ethanol, rinsed and dipped briefly in 1 mM lavamisole in phosphate buffered saline (PBS), then washed in water (2 min) and rinsed once more in PBS. The sections were next treated with pronase (10–14 min) in a PBS solution, rinsed in PBS, and postfixed in paraformaldehyde. Following a 1–3 min wash in PBS-Triton X-100, incubation in glycine, and brief rinses in ethanol, hybridization was carried out by applying a commercially available CMV or HSV DNA probe (Enzo Biochemicals) in diluent to each slide and incubating the sections, initially in a 91° C vapour water bath for 12 min, then a 37° C water bath for 3 h or overnight. Subsequent washes with PBS-Triton X-100 and treatment of slides in NaCl/Na citrate solution-formamide mixture were followed by addition to the slides of Detek-1-alkaline complex (Enzo Biochemicals) and developing the reaction product with 5-bromo-4-chloro-3-indoyl phosphate p-toluidine salt (BCIP, American Research Products Company) and nitroblue tetrazolium chloride (NBT, Sigma) to yield a dark blue colour in loci where the CMV or HSV genomes were present. Finally, sections were lightly counterstained with eosin. For all hybridization runs, appropriate positive and negative control slides were simultaneously stained and examined. The HSV probe was from a gene fragment containing the thymidine kinase (TK) genes of HSV I cloned into the Bam H1 site of pBR322. Insert size was 3.5 kb including the TK coding region and approximately 2.5 kb of flanking sequences. The CMV probe was from a mixture of two clones of CMV sequences in the Bam H1 site of pBR322 with insert sizes of 17.2 kb and 25.2 kb, and does not cross-hybridize with HSV I, HSV II, Epstein-Barr virus, or components of the normal human genome (Dr W W. Grody, personal communication).

Colocalization (CMV, HIV, MGN) studies

In 11 brains examined, at least 23 tissue blocks from predetermined regions of brain, sampled using a blocking diagram, were available. All sections were examined for the presence or absence of (1) CMV inclusions, (2) multinucleate giant cells characteristic of HIV infection of the brain, hereafter referred to as HIV-GC (Sharer *et al.*, 1985; Budka, 1986; Koenig *et al.*, 1986; Navia *et al.*, 1986; Kato *et al.*, 1987), and (3) typical MGNs. These data were tabulated and localization within the same tissue block of a combination of any two or all three of the microscopic lesions was assessed. Brain tissue from 7 of the 11 patients showed CMV (with or without MGNs) in the absence of HIV-GC, while in 4 cases there was evidence of both HIV and CMV infections within the same brain. Use of HIV-GC as a marker for HIV infection of brain probably underestimates the amount of HIV genome or antigen present, in situ hybridization or immunocytochemistry being more sensitive techniques (Wiley *et al.*, 1986*a*). These conventional markers for CMV and HIV infection were, however, felt to be most practical in view of the large amount of tissue to be screened.

Clinical data

Where available, case notes and clinical autopsy protocols were reviewed, with particular attention to clinical signs and symptoms, results of neuroimaging studies, and data on cerebrospinal fluid (CSF) analysis. The amount of information retrievable varied greatly among the patients. CSF data were available from 12 patients. Clinical and/or pathological information on a small number of these patients has been presented in other publications (Pepose *et al.*, 1984; Clark and Vinters, 1987; Vinters *et al.*, 1987), and data on all of them have been included in reviews of the UCLA experience with neuropathological complications of AIDS (Anders *et al.*, 1986*a*, *b*; Vinters *et al.*, 1989).

RESULTS

The 31 patients studied are representative, in terms of race and risk factors for AIDS, of the patients with this clinical diagnosis who have come to necropsy at our centre. All adult patients were male, and their mean age at death was 39.4 yrs. The single child was a 6.5 yr old girl with AIDS contracted by maternal prenatal transmission. Common systemic infections documented in this group are summarized in Table 1. Half the adult patients and the child had Kaposi's sarcoma.

In 26 of 31 patients, the nervous system was one of several sites throughout the body involved by CMV infection (Table 2). Other locations in which CMV was likely to be found included the lungs, retina, adrenal glands, and gastrointestinal tract, in roughly decreasing order of frequency. The pituitary gland was involved in 1 case, and is rarely a location in which CMV is discovered even with widespread

TABLE 1 CMV ENCEPHALITIS COMMON SYSTEMIC INFECTIONS

Infection	*No. of patients*
Pneumocystis carinii pneumonia	24
Candida albicans	22
Mycobacterium avium-intracellulare	12
Herpes simplex (usually perianal)	8
Syphilis	8
Hepatitis B	8
Gonorrhoea	6
Giardiasis	5
Cryptosporidiosis	5
Amoebiasis	4
Aspergillosis	3
Cryptococcosis	2

All infections documented clinically and/or at autopsy

TABLE 2 CMV ENCEPHALITIS OTHER ORGANS INVOLVED BY CMV

Lungs	19	Thyroid	3
Retina	14	Spleen	3
Adrenal glands	14	Lymph node(s)	2
Gastrointestinal tract	11	Prostate	2
Liver	4	Kidney	1
Pancreas	3	Pituitary (anterior)	1

Isolated brain involvement at necropsy (5 cases); CMV cultured from blood (1 case); 'clinically proven' CMV infection (1 case).

TABLE 3 CMV ENCEPHALITIS ASSOCIATED NEUROPATHOLOGY

A Possibly/definitely related to CMV infection	
Choroid plexitis	2
Leptomeningitis/meningo-radiculitis	5
Microglial nodules	29
Vasculitis	4
Necrotizing leucoencephalopathy	2
Necrosis/infarcts	3
Myelopathy (multifocal)	1
B Unrelated to CMV infection	
Infectious	
Toxoplasmosis	3
Cryptococcosis	1
HIV-GC[1]	7
MAI[2]	4
Herpes simplex	1
Other	
Isolated cerebral lymphoma[3]	5
Dystrophic and/or vascular calcification	8
Vacuolar myelopathy	4
Focal pontine leucoencephalopathy or central pontine myelinolysis	2

[1]HIV-GC = giant cells characteristic of HIV infection of brain, [2]MAI = mycobacterium avium-intracellulare; [3]includes 1 probable case (tumour very necrotic) and 1 definite case associated with cerebral lesions of lymphomatoid granulomatosis.

viral infection (Ferreiro and Vinters, 1988). Of the 5 patients who showed isolated CNS involvement by CMV, the virus had previously been cultured from the blood of 1 patient and 1 individual was said to have clinically proven CMV infection, although details of this documentation were not available.

Table 3 summarizes the neuropathological abnormalities present among the cases studied. The neuropathological findings have been divided into those apparently related to CMV infection, as judged by their proximity to typical CMV inclusions or virus demonstrated by in situ hybridization, and those not obviously associated with CMV infection. The 'unrelated' pathology may, however, in part result from immunosuppression induced by the CMV infection itself (Bale, 1984). The most common association was between the presence of CMV and MGNs in the same brain, often in the same tissue section (*see* below). The frequent finding of CMV inclusions at the centres of MGNs (Vortel and Plachý, 1968; Dorfman, 1973; Nielsen *et al.*, 1984; Anders *et al.*, 1986*b*; Morgello *et al.*, 1987) makes this association a compelling one in some instances. In small numbers of cases, CMV inclusions were found within or adjacent to foci of necrotizing leucoencephalopathy or small foci of parenchymal necrosis or infarcts with variable degrees of acute or chronic inflammation (fig. 1). Vasculitis or perivascular inflammation related to

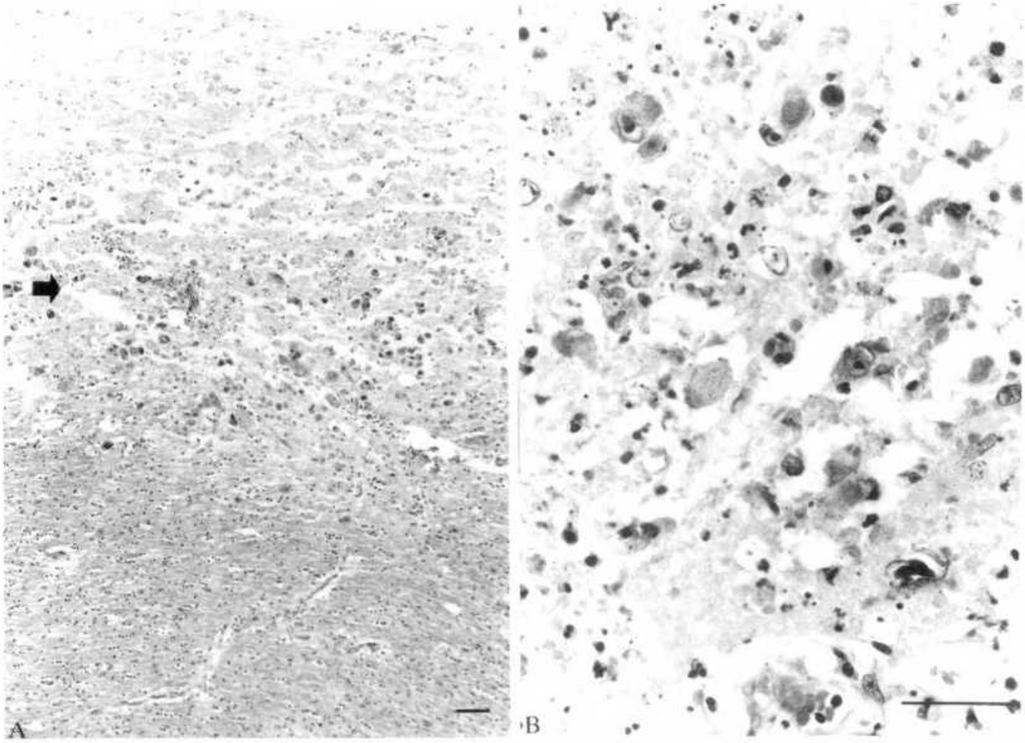


FIG. 1. *Case 2* (Table 5). A, periventricular region (cavity of lateral ventricle at top) shows periventricular necrosis, and CMV encephalitis deep to this area (arrow). Relatively normal white matter at bottom. Haematoxylin and eosin. Bar = 100 μm. B, detail of periaqueductal region shows CMV inclusions, tissue vacuolation and scattered inflammatory cells including polymorphonuclear leucocytes. Haematoxylin and eosin. Bar = 50 μm.

CMV was found in 4 patients and has previously been described (Goodman and Porter, 1973; Koeppen *et al.*, 1981). Rarely, CMV was found in the cytoplasm of endothelial or smooth muscle cells. In situ hybridization for CMV occasionally localized CMV DNA to microvascular endothelial cells (fig. 2), although this was not always accompanied by vasculitis. Chronic leptomeningitis, often with definite CMV inclusions within the subarachnoid inflammatory infiltrate, was found in 5 patients. Choroid plexitis (fig. 3) was noted in 2 patients, who showed severe ependymal and subependymal involvement by CMV.

Neuropathological findings not obviously related to CMV infection of neural parenchyma are summarized in part B of Table 3. A rather striking coincidence was noted between CMV infection and the presence of multinucleated giant cells (fig. 4) characteristic of HIV infection of the brain (HIV-GC) in 7 cases. In our autopsy experience with AIDS, we have only encountered this giant cell encephalitis in 17 patients (Vinters *et al.*, 1989). This co-occurrence of two viral infections is discussed further below. The second interesting association was between CMV infection of the brain and cerebral lymphoma, the latter also being an unusual finding in our population of AIDS patients.

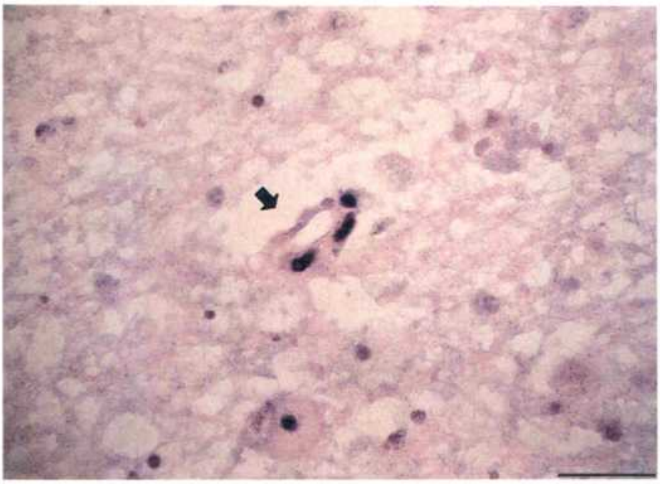


FIG. 2. *Case 3* (Table 5). In situ hybridization for CMV showing a microvessel with CMV genome within endothelial cells (arrow). Other scattered cells show reaction product, and the surrounding tissue shows vacuolation. Bar = 50 μm.

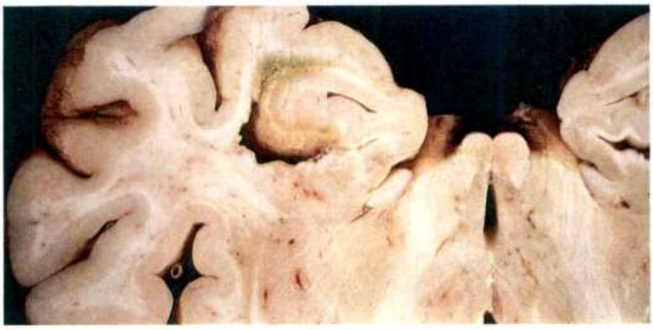
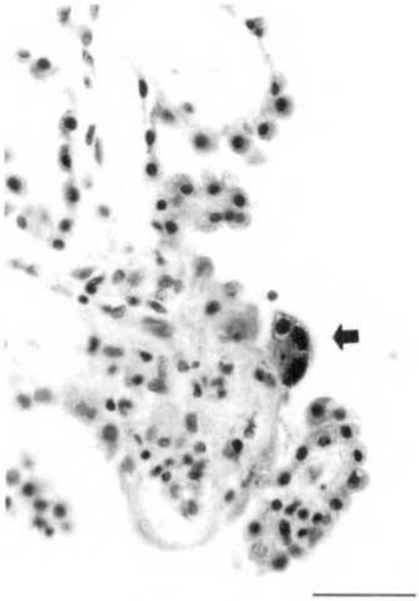


FIG. 7. Patient was markedly jaundiced before death. At brain cutting, green discolouration was seen in foci of CMV encephalitis and ependymitis around temporal horn of right lateral ventricle.



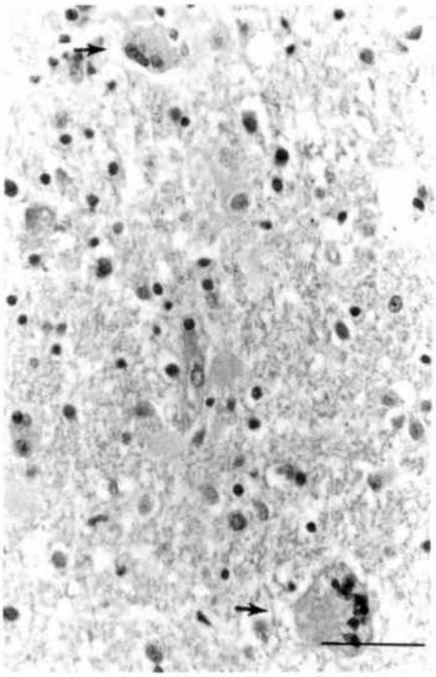


FIG. 3. (*Left.*) Choroid plexitis. A frond of choroid plexus shows several characteristic epithelial CMV inclusions (arrow) and a few scattered inflammatory cells in underlying vascular stroma. Haematoxylin and eosin. Bar = 50 μm.

FIG. 4. (*Right.*) Giant cells with granular or foamy cytoplasm and multiple peripherally displaced nuclei (arrows) characteristic of HIV infection of the brain. Haematoxylin and eosin. Bar = 50 μm.

In view of the continuing controversy surrounding the pathogenesis of the frequently observed MGN encephalitis in the CNS of AIDS patients, we assessed the number of tissue blocks in selected cases that contained MGNs, CMV inclusions and/or HIV-GC. Table 4 summarizes the results of such a survey in 7 patients in whom CMV was the only or major opportunistic pathogen identified within the brain at necropsy. In these relatively 'pure' cases of CMV meningoencephalitis, CMV inclusions were identified in over 25% of the blocks examined, while MGNs were present in over 40%. The two types of lesion colocalized (i.e., were found within the same tissue block or section) in over 12% of the sections. However, analysis of the data using the χ^2 test failed to establish a significant association between the two findings.

When this survey was extended to include the 4 patients with both CMV and HIV-GC in the brain (Table 5), CMV and MGN were seen to colocalize within roughly the same percentage of tissue sections or blocks, while HIV-GC and MGN colocalized in almost 20% of sections. CMV and HIV-GC were seen together in over 10% of sections examined, while all 3 microscopic lesions

TABLE 4 ASSOCIATION BETWEEN CMV* AND MGN**

Case	*Total no. blocks*	*CMV*	*MGN*	*CMV and MGN*
1	23	2	12	1
2	23	12	16	7
3	23	6	21	6
4	23	14	8	5
5	24	2	12	2
6	23	2	2	1
7	31	6	0	0
Totals	170	44	71	22
Percentage	—	25.9	41.8	12.9

*CMV = cytomegalovirus; **MGN = microglial nodules.

TABLE 5 ASSOCIATION: CMV, MGN, AND HIV-GC*

Case	*Total no. blocks*	*CMV*	*MGN*	*HIV-GC*	*CMV and HIV-GC*	*CMV and MGN*	*HIV-GC and MGN*	*CMV, MGN and HIV-GC*
1	26	9	11	11	2	3	8	1
2	31	16	20	12	5	9	10	4
3	31	13	8	7	5	3	1	0
4	30	2	5	14	0	0	3	0
Totals	118	40	44	44	12	15	22	5
Percentage	—	33.9	37.3	37.3	10.2	12.7	18.6	4.2

*HIV-GC = giant cells characteristic of HIV infection of brain.

colocalized in 4.2% of sections. χ^2 analysis of the data showed the only statistically significant ($P = 0.05$) association to be between HIV-GC and MGN. In 2 additional patients, whose brains contained both CMV and HIV-GC, the two types of microscopic lesion were also frequently found in the same tissue section. Typical Cowdry type A CMV inclusions within otherwise characteristic HIV-GC were never seen within brain tissue; we thus have no good morphological evidence that the viruses colocalize within the same cell. In 1 patient (Table 5, Case 4), however, the adrenal gland contained several cells with nuclei displaced peripherally around the cytoplasm (possibly representing an extracerebral HIV-GC) and a typical CMV type intranuclear inclusion (fig. 5).

In virtually every case, the microscopic findings were much more extensive than had been predicted from the gross appearance of the brain and spinal cord at the time of necropsy or brain cutting. Rarely, CMV inclusions were seen in tissue sections without any inflammatory or tissue response, a finding previously identified by others (Morgello *et al.*, 1987). The affinity of CMV for ependymal surfaces (fig. 6) and its tendency to spread from these surfaces in a ventriculofugal fashion

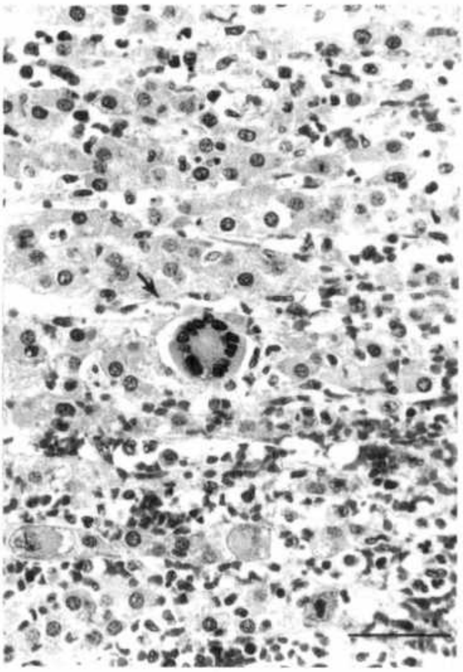


FIG. 5. *Case 4* (Table 5). Adrenal cortex showing a single giant cell (arrow) with a typical Cowdry 'A' intranuclear inclusion and smaller nuclei arranged around the periphery of the slightly granular cytoplasm. Haematoxylin and eosin. Bar = 50 μm.

(Hawley *et al.*, 1983; Post *et al.*, 1986; Wiley *et al.*, 1986*b*) have been described. This phenomenon was illustrated at the time of brain cutting in a patient who had been severely jaundiced but had experienced relatively nonspecific neurological complaints before death. Coronal sections of the cerebral hemispheres revealed a green discolouration of the ependymal lining in the region of the temporal horn of the right lateral ventricle (fig. 7, p. 251). Sections of this region showed large numbers of CMV inclusions in and deep to the ependyma. In addition to CMV localization within ependyma of the temporal horn or body of the lateral ventricle, it was frequently encountered in the floor of the fourth ventricle. In situ hybridization has shown CMV DNA within both ependymal and subependymal cells in some cases.

Several conspicuous examples of gross and microscopic neuropathology merit brief comment. Figs 8 and 9 demonstrate a severe degree of haemorrhagic ventriculitis (fig. 8) and haemorrhagic necrosis around the cerebral aqueduct (fig. 9) in a patient who also had widespread CMV encephalitis associated with patchy demyelination of the central white matter. Widespread CMV was confirmed by

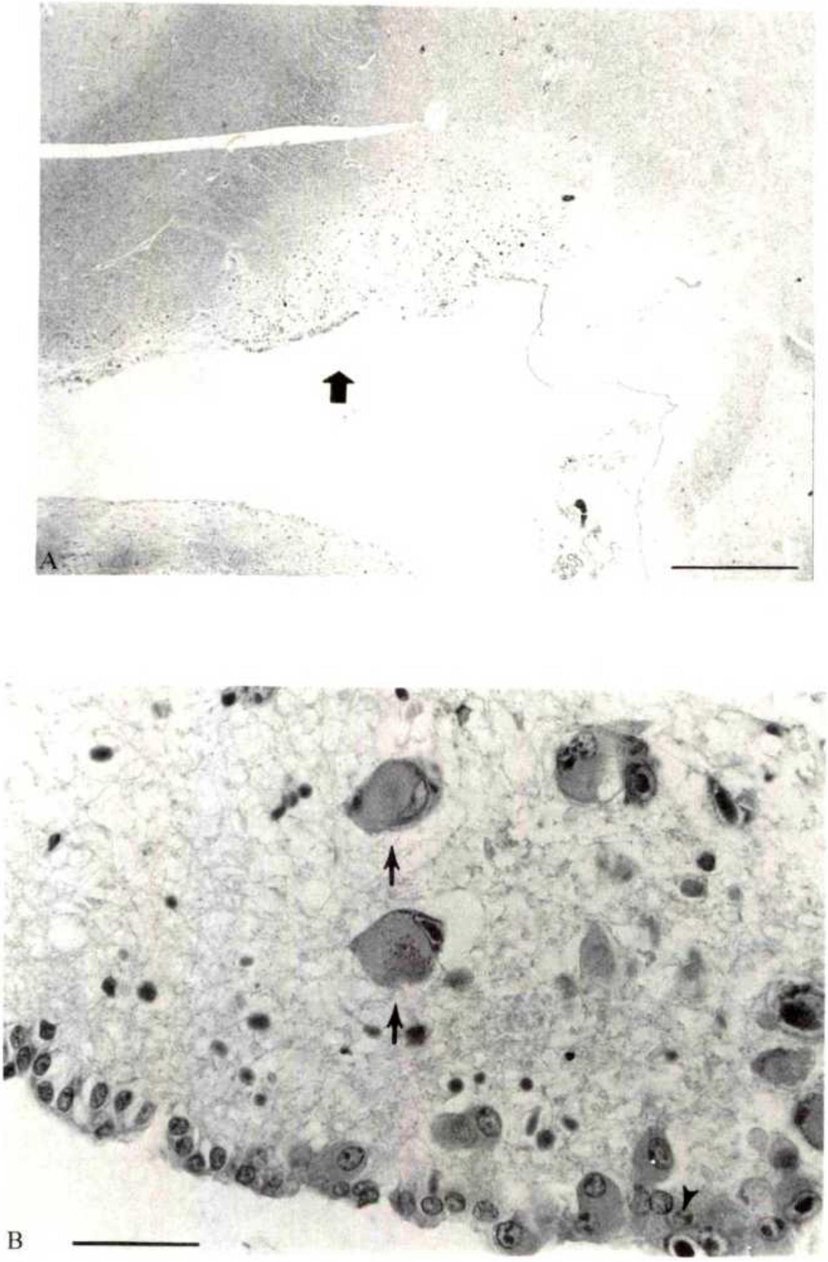


FIG. 6. A, low power view of lateral ventricle showing extensive ulceration of ependymal lining and slight increase in underlying cellularity (arrow). Bar = 1 mm. B, magnified view showing characteristic CMV inclusions within ependymal cells (arrowhead) and in subependymal cells (arrows) with surrounding spongiosis of tissue. Haematoxylin and eosin. Bar = 50 μm.

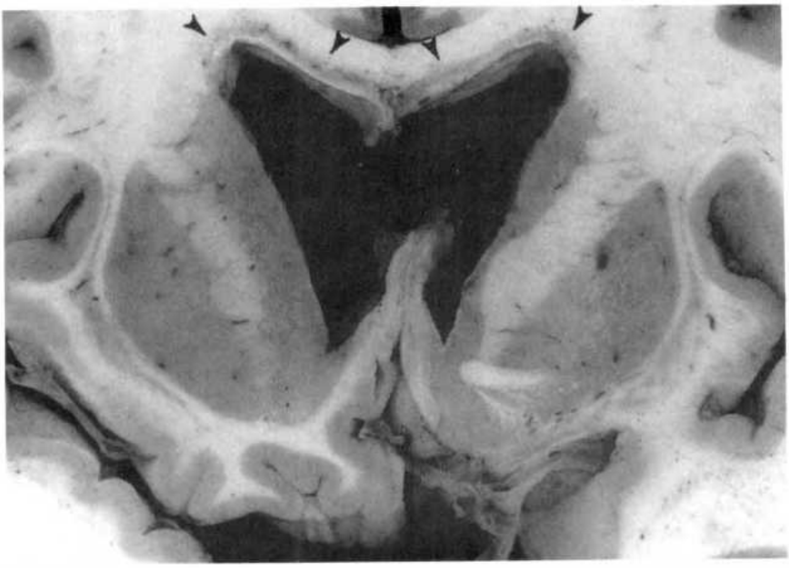


FIG. 8. Lateral ventricles are dilated and show haemorrhagic necrosis deep to the ependymal surface (arrowheads), as well as necrosis of the septum pellucidum.

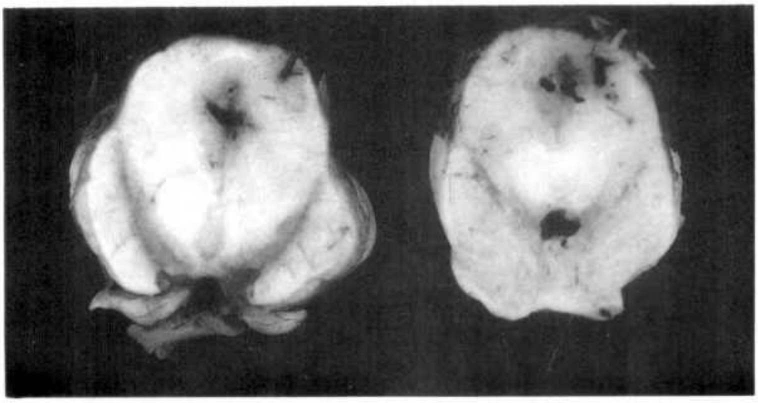


FIG. 9. Same patient as in fig. 8. Note haemorrhagic necrosis (secondary to CMV encephalitis) around the cerebral aqueduct and fourth ventricle, virtually obliterating these structures.

hybridization studies (fig. 10). A 44-yr-old man with findings suggestive of intrinsic spinal cord abnormalities was treated with Ganciclovir (DHPG, 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl] guanine) after CMV was isolated from his CSF. Neurological improvement resulted, but autopsy disclosed foci of 'old' necrotizing myelopathy (fig. 11) in the thoracolumbar spinal cord (hybridization studies for CMV and HSV were negative). The myelopathy was unlike the vacuolar myelopathy or long tract degeneration (Horoupian *et al.*, 1984; Goldstick *et al.*, 1985; Petito *et al.*, 1985) described in patients with AIDS. Myelitis caused by CMV and HIV has been described in a patient with AIDS (Tucker *et al.*, 1985).

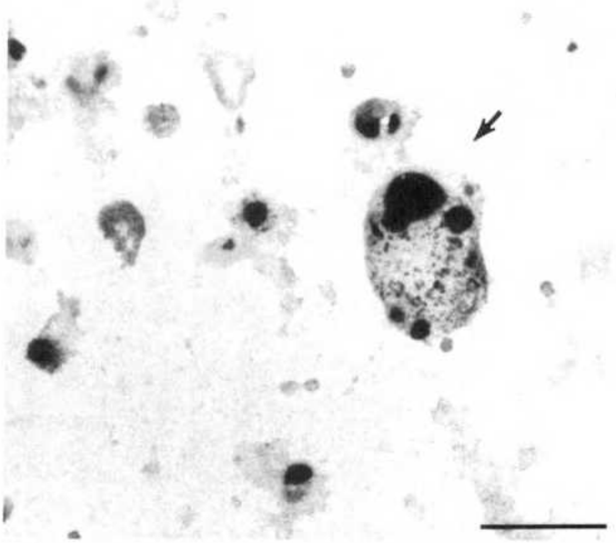


FIG. 10. Periventricular white matter. In situ hybridization for CMV showing reaction product in several cells, especially one large cell (arrow) which shows both nuclear and cytoplasmic positivity. Bar = 50 μm.

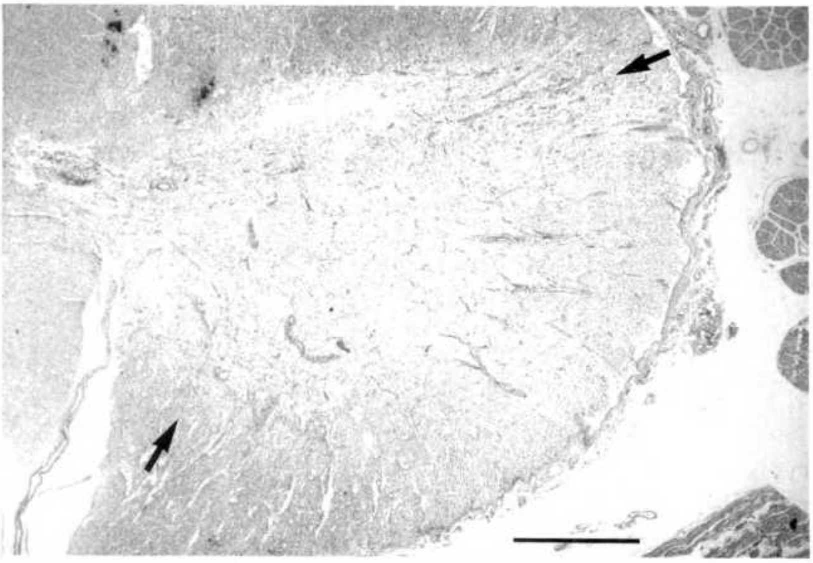


FIG. 11. *Case 3* (Table 5). Lumbar spinal cord showing poorly demarcated area of old necrosis within both grey and white matter (arrows). Ventral median fissure seen at lower left. No CMV or HSV inclusions were identified and hybridization studies were negative. Haematoxylin and eosin. Bar = 1 mm.

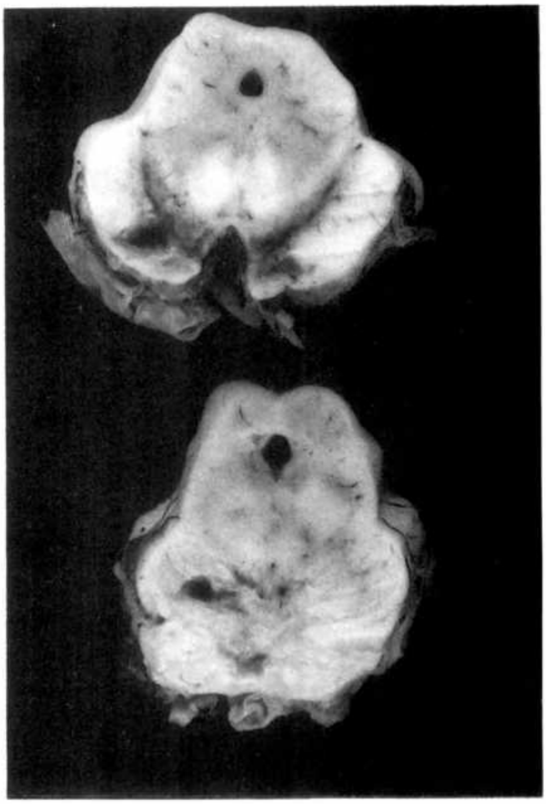


FIG. 12. *Case 7* (Table 4). Midbrain and pons showing asymmetric poorly defined regions of necrosis in medial cerebral peduncles and basis pontis, respectively. Numerous CMV inclusions were identified in and around these areas.

Fig. 12 shows necrotic foci in the medial cerebral peduncles and the basis pontis of another patient, within which numerous CMV inclusions were found. Other cystic and necrotic lesions with old haemorrhage throughout the cerebral hemispheres failed to show evidence of CMV infection. A 27-yr-old man with a rapidly evolving paraplegia died 7 wks after symptom onset. The spinal cord showed severe necrotizing meningoradiculitis with a component of microvascular thrombosis apparently caused by CMV (fig. 13), while the brain showed ependymal and subependymal CMV and typical HIV type giant cells.

A 44-yr-old male died with AIDS complicated by severe dementia, and the presence of a cerebral lesion treated (by chemotherapy and radiotherapy) as probable lymphoma. Necropsy disclosed a necrotic cerebral lesion possibly representing necrotic lymphoma, and numerous CMV inclusions and HIV giant cells, together with extensive reactive change (fig. 14) in ependymal and subependymal tissues. Electron microscopy of brain tissue revealed both intranuclear CMV particles in various stages of maturation and typical HIV virions (fig. 15) (Meyenhofer *et al.*, 1987). The two viruses were not identified within a single cell, however.

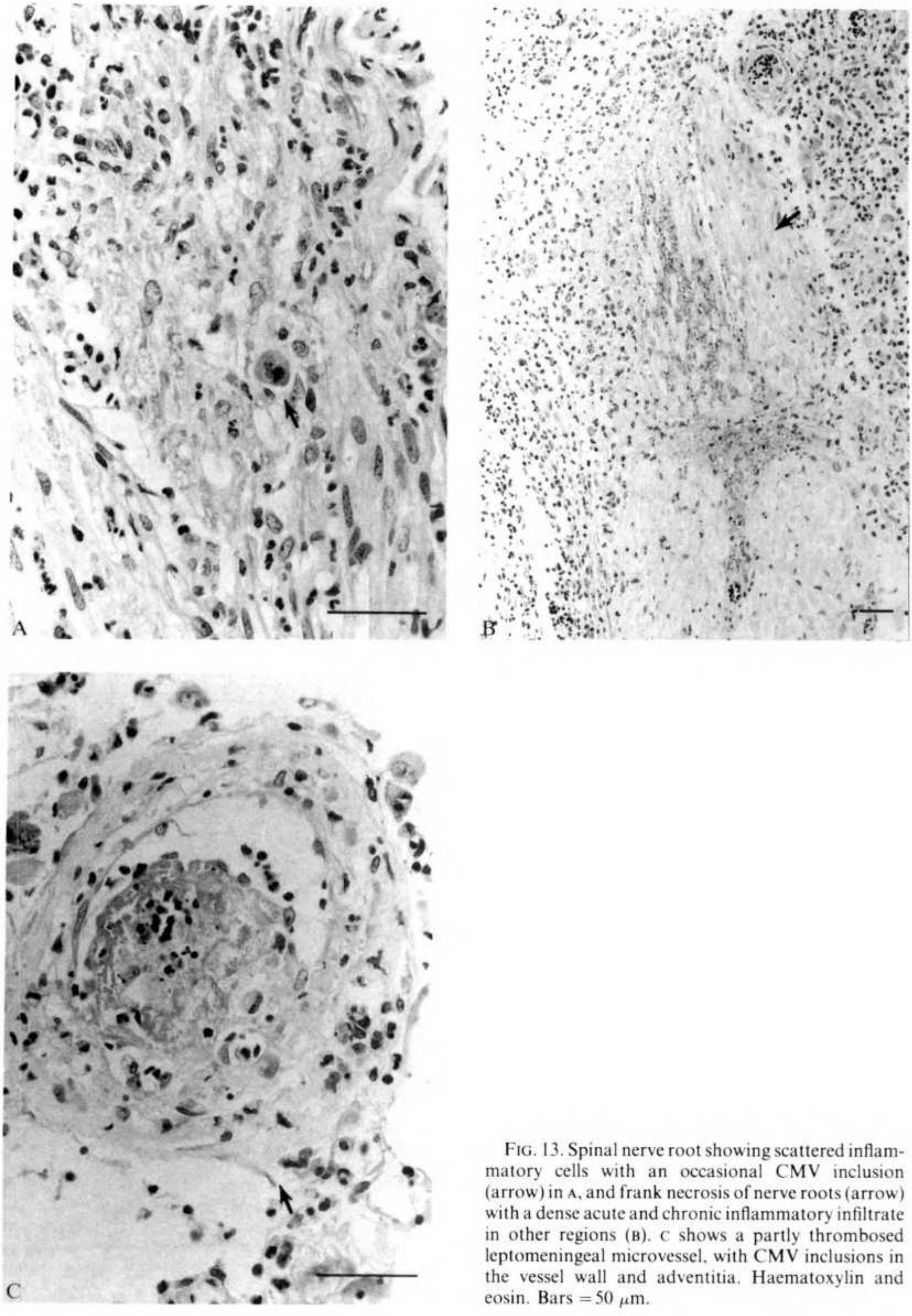


FIG. 13. Spinal nerve root showing scattered inflammatory cells with an occasional CMV inclusion (arrow) in A, and frank necrosis of nerve roots (arrow) with a dense acute and chronic inflammatory infiltrate in other regions (B). C shows a partly thrombosed leptomeningeal microvessel, with CMV inclusions in the vessel wall and adventitia. Haematoxylin and eosin. Bars = 50 μm.

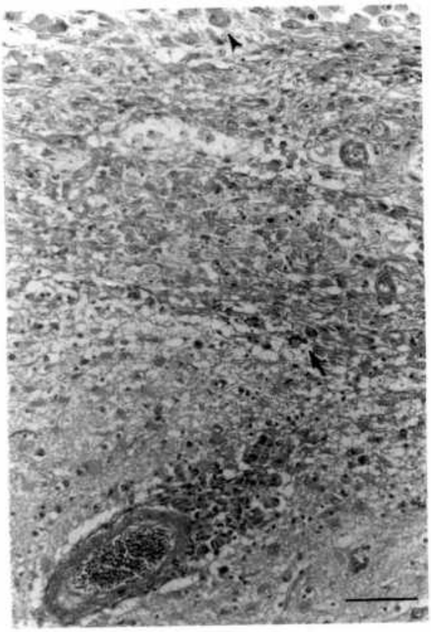


FIG. 14. Periventricular region around lateral ventricle showing numerous CMV inclusions (e.g., arrowhead) at top, closest to ventricle, surrounded by necrosis with histiocytes. Deeper within parenchyma there is pronounced reactive astrogliosis. Perivascular histiocytes and scattered HIV-GC (arrow) are present. Haematoxylin and eosin. Bar = 100 μm.

Clinicopathological correlation

Precise clinicopathological correlation with regard to neurological signs and symptoms attributable to CMV infection is often difficult. The immunosuppression causes a plethora of systemic abnormalities, especially opportunistic infections, that may mask focal or diffuse neurological signs and symptoms or tempt a clinician into interpreting subtle neurological abnormalities as being on the basis of sepsis or metabolic derangement. In many cases lesions caused by CMV constitute only one of several types of neuropathology in a single patient. Subtle lesions related to CMV may also be clinically 'silent'. Only half of our patients had 'pure' CMV infection of the nervous system, and the others had significant other neuropathology (*see* Table 3). Finally, the lesions related to CMV infection, though often florid microscopically, may not show up on imaging studies. A review of the results of available imaging studies (usually CT and MRI) in our 31 patients showed that 19 were thought to have no significant abnormality, while an additional 8 had cerebral cortical atrophy with or without ventricular enlargement, which was felt to be nonspecific. This was usually reflected in the normal appearing or slightly atrophic brains seen at necropsy. Even in individuals with severe involvement of brain, spinal cord or nerve roots by inflammatory CMV lesions, the aetiological agent was often not clinically suspected.

CSF data were available from 17 determinations in 12 patients (7 with pure CMV involvement) and showed a relatively nonspecific picture. The protein content was frequently modestly or markedly elevated (up to 8.06 g/l) while

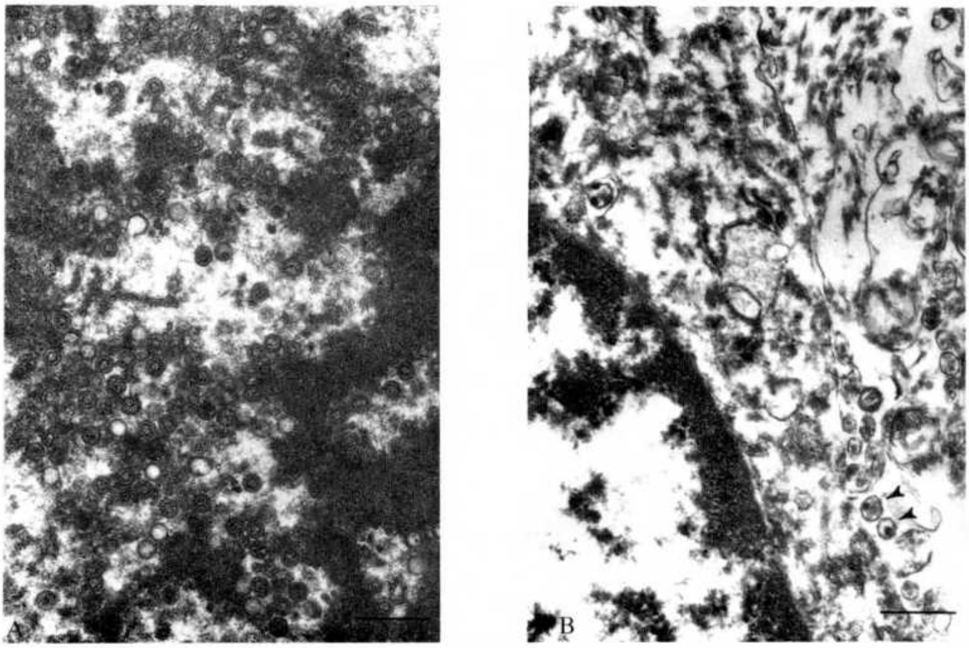


FIG. 15. Same patient as in fig. 14. Ultrathin sections, electron microscopy. A, intranuclear CMV virus particles in various stages of maturation. B, typical HIV particles (arrowheads) apparently budding from surface of a cell membrane. Bars = 500 nm.

glucose was often moderately decreased, in the range of 2.8 mmol/l. In 1 patient, IgG was markedly elevated to 0.098 g/l (reference interval < 0.01–0.045 g/l). Cell counts were variable, ranging up to 12,000 WBC/μl with a differential that showed lymphocyte predominance in 2 determinations, and a preponderance of polymorphonuclear leucocytes or band forms in 7. CMV was cultured from the CSF of 2 patients. It is known in general to be a difficult undertaking unless pursued aggressively (Edwards *et al.*, 1985).

DISCUSSION

CMV infection of the nervous system occurs in immunocompromized as well as normal adults and children (Schneck, 1965; Schober and Herman, 1973; Hotson and Pedley, 1976; Phillips *et al.*, 1977; Kauffman *et al.*, 1979; Bale, 1984; Lerner and Tapper, 1984; Zaia and Lang, 1984; Cohen and Corey, 1985), and has been well documented in AIDS patients (Vital *et al.*, 1985; Muñoz *et al.*, 1987). We have been impressed by the heterogeneous neuropathology that this virus produces in patients with AIDS. Other authors' series, with a different emphasis, have also described this complication in AIDS patients (Post *et al.*, 1986; Morgello *et al.*, 1987).

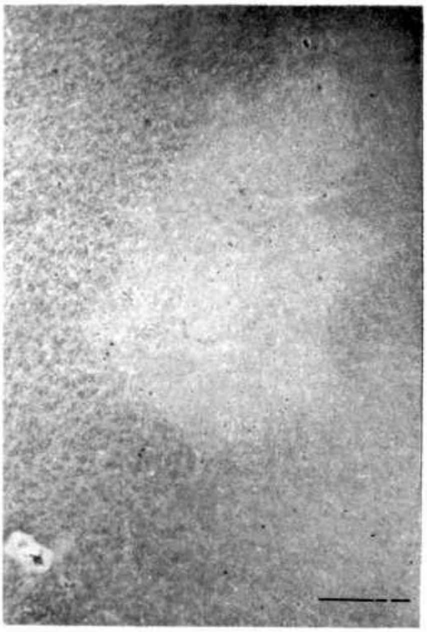


FIG. 16. Centrum semiovale showing relatively well-demarcated oval focus of myelin loss. Punctate structures (CMV inclusions at higher magnification) can just be discerned at centre and margins of the lesion, which also showed axon loss on appropriate stains. Weil stain. Bar = 1 mm.

CMV localizes in the nervous system in AIDS patients who in general have evidence of widespread CMV infection. Even the small number of patients (Table 2) we have identified with isolated CNS involvement by CMV may have yielded evidence of disseminated or multifocal infection within the body, had this been sought more aggressively. In half of our cases, CMV infection was only one component of the significant neuropathology. Particularly intriguing is the association with primary cerebral lymphoma that we have encountered. CMV infection of the nervous system has been seen in less than 20% of AIDS patients at UCLA, whereas evidence of systemic CMV infection is noted in over half of the patients autopsied (Vinters *et al.*, 1989).

CMV tends to localize to ependymal surfaces and to move from these regions in a ventriculofugal fashion (Wiley *et al.*, 1986*b*). CMV-related ventriculoencephalitis can sometimes be suspected on gross inspection of the brain (figs 7, 8). In 1 patient, necrosis around the cerebral aqueduct apparently contributed to the development of obstructive hydrocephalus. The overall spectrum of CMV-related microscopic lesions has been summarized by Morgello *et al.* (1987). The occurrence of CNS demyelination related to the presence of CMV in the absence of axonal injury (i.e., frank necrosis) has been described in several patients (Moskowitz *et al.*, 1984), although to date this association remains anecdotal. Ill-defined areas of demyelination (fig. 16) and inflammation around foci of CMV encephalitis were also commonly observed in our material, however. It is clear from all studies that CMV in the nervous system may induce a relatively trivial inflammatory response and may produce no specific neurological abnormalities.

In the CNS of patients within whom CMV constituted the sole or primary cause of neuropathology, MGNs were frequently encountered although within these brain tissues, CMV and MGNs were found together in only half the number of blocks in which CMV was localized histologically. In these same cases (*see* Table 4) MGNs were encountered more frequently than were typical nuclear and cytoplasmic inclusions of CMV. Using the multinucleate giant cell characteristic of HIV infection of the neural parenchyma as a marker for the latter, evidence of both CMV and HIV infection within the same brain was discovered in 7 cases, and the two types of microscopic lesion were often found in close physical association. MGNs were found together with HIV-GC more commonly than with CMV, and only the former association was statistically significant, although our study supports the conclusion that the commonly observed low grade MGN encephalitis seen in patients with AIDS can be caused either by CMV or HIV independently or in combination. It also provides some evidence for the hypothesis that CMV encephalitis may bring macrophages containing HIV into the brain, although the mere physical proximity of the two viruses (which our study shows) does not prove that one agent causes the other to enter the brain. A mechanism by which HIV enters the CNS is not otherwise well established (Vinters *et al.*, 1989; Wiley *et al.*, 1987). Against the view that CMV leads to HIV infection of the nervous system is the discovery of HIV in brain tissue and CSF early in the course of the syndrome, presumably before the occurrence of opportunistic CMV infection (Gabuzda and Hirsch, 1987).

The single example of necrotizing inflammatory polyradiculoneuropathy with extensive radicular vascular involvement and thrombosis secondary to microvessel wall infection illustrates one mechanism whereby a Guillain-Barré-like clinical syndrome can occur in these patients. The association of Guillain-Barré polyneuropathy with herpes viruses and particularly CMV infection has anecdotal support (Klemola *et al.*, 1967; Kabins *et al.*, 1976; Schmitz and Enders, 1977; Bale *et al.*, 1980), but the extensive necrosis in the nerve roots of this patient suggests that neurological recovery may have been slow if even possible. Other patients with AIDS and CMV infection have been found to show radiculomyelitis (Bishopric *et al.*, 1985; Eidelberg *et al.*, 1986; Behar *et al.*, 1987), but with less extensive necrosis and vascular involvement. The question also arises of how many examples of peripheral neuropathy, which is common in AIDS patients (Levy *et al.*, 1985; Mah *et al.*, 1987; Parry, 1988), result from more proximal nerve root involvement by CMV.

Unfortunately, these data do not provide clinical guidance as to ascertainment of AIDS patients in whom CMV infection might be the cause of neurological morbidity, except to indicate that such infection is common. Clinical findings, imaging studies and examination of CSF provide little definitive information to guide therapy.

CMV, as this study indicates and others have shown (Myerson *et al.*, 1984; Wiley *et al.*, 1986*b*; Morgello *et al.*, 1987), has a propensity to infect one or more of several cell types in or outside the nervous system. The mechanism of CMV infection of brain cells has also been studied in tissue culture (Bale *et al.*, 1987). We and others (Wiley *et al.*, 1986*b*; Clark and Vinters, 1987) have previously shown some cytomegalic cells to stain positively with an immunohistochemical method for GFAP. Based on a single case study, the suggestion has been made that CMV within brain shows a lower density of complete virions per cell and a higher proportion of defective viral particles than are found in other organs, such as lung (Muñoz *et al.*, 1987). The reasons for this will undoubtedly become clear as the molecular virology of CMV infection becomes more clearly understood (Sissons *et al.*, 1986). The study of CMV encephalitis in AIDS will also be facilitated by the recent observation of this form of encephalitis in Rhesus monkeys infected with the lentivirus SIV/Delta (Baskin, 1987).

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BOOK REVIEWS

The Molecular Biology of Neurological Disease. Edited by R. N. Rosenberg and A. E. Harding. 1988 Pp. 263. London: Butterworths. Price £35.00.

Advances in molecular genetics and recombinant DNA are having a revolutionary effect on the prevention of genetic disease and on our understanding of disease processes. To date some 4,000 disorders are recognized as being genetic and of these, over a thousand have been localized to particular chromosomes and even to specific sites on chromosomes. Furthermore, gene probes are becoming available for many of these disorders. These developments have led to novel approaches to detecting presymptomatic cases of autosomal dominant disorders, female carriers of X-linked disorders and prenatal diagnosis. The hope is that, progressing from the identification of a DNA marker for a disease, it will be possible eventually to isolate the responsible gene and then to identify and characterize its product. This would lead to a better understanding of pathogenesis and, perhaps, one day rational therapy. These exciting developments are nowhere better illustrated than in the case of neurological disorders and are very well charted in this new addition to Butterworth's series of Medical Reviews.

The opening chapter by the editors themselves outlines the basic principles and methods of molecular genetics. This is a model of clarity and explains many of the new techniques and concepts. A glossary of terms, however, would probably also be helpful to many new to the field.

It has been estimated that 70,000 to 100,000 proteins are expressed in a brain cell from about 3×10^5 genes. The identification and characterization of these genes therefore presents a formidable task but the rewards are considerable, for not only will information in this field lead to a better understanding of disease processes, but may one day throw light on mechanisms of learning and memory. Several chapters, which will mainly be of interest to readers with a more scientific bent, plot approaches being pursued to characterize brain messenger RNAs, chemical neurotransmitters and various regulatory proteins, such as nerve growth factor, platelet-derived growth factor, neural cell adhesion molecule and laminin. The problem is that not only are there so many RNAs in brain and their function unknown, but many are expressed in very low levels. Gene expression in skeletal muscle is also interestingly reviewed—a subject likely to prove of particular relevance now that the protein abnormality in Duchenne muscular dystrophy has been identified. Insights through molecular genetics into viral tropism are discussed. Details of the interaction between host susceptibility genes and viral genes are beginning to emerge which involve host cell receptors and viral cell attachment proteins and enhancers.

The second part of the book deals with specific disorders and groups of disorders; Joseph's disease, Huntington's disease, muscular dystrophy, mitochondrial disorders (myopathies and Leber's optic atrophy) and retinoblastoma. Finally, the detection of viral genes in neurological disorders and genetic susceptibility are discussed. This latter part of the book will be of most immediate interest to practising physicians. The chapter on muscular dystrophy is particularly pragmatic in its approach and should be very helpful to physicians who manage and give genetic advice in affected families.

In a multi-authored work there is inevitably repetition. Alzheimer's disease, for example, is discussed in various guises by several authors. A separate chapter devoted to this disorder would have been well justified in view of its importance and current interest. The index is also a little disappointing. But these are minor peccadillos. The book provides an excellent up-to-date review of the contribution being made by molecular genetics to neurological disease. These new approaches to diagnosis will soon become as commonplace in neurological practice as the tendon hammer and tuning fork.

ALAN EMERY

Facial Dyskinesias. *Advances in Neurology*, Volume 49. Edited by Joseph Jancovic and Eduardo Tolosa. 1987. Pp. 560. New York: Raven Press. Price $121.50.

This book contains much to interest the general neurologist as well as the specialist in movement disorders. It should also be a useful source of selective reading for ophthalmologists, psychiatrists, ENT specialists, and all those involved in the surgical treatment of patients with cranial dyskinesias. There is extensive coverage of the more common disorders of movement affecting the head and neck: blepharospasm, tics, oromandibular dystonia, tardive phenomena, chorea, hemifacial spasm, torticollis and various types of tremor. Also discussed are less common focal syndromes such as palatal myoclonus, spasmodic dysphonia and bruxism. There are useful general review chapters on facial movements in epilepsy, the so-called apraxias of eye-opening and closure, and the various causes of involuntary vocalization and self-mutilation in the orofacial region and elsewhere. There are sections on facial anatomy and neurophysiology, and on what little is known about the pathology of cranial movement disorders. A series of chapters in the latter part of the book deals with the complex neuropharmacology of tardive phenomena and cranial dystonias. There are four contributions on the more common uses of botulinum toxin. Included in one volume, therefore, are authoritative reviews of a wide range of conditions with which many neurologists may feel familiar but slightly uncomfortable.

The first chapter by Joseph Jancovic is an excellent introductory review of the topic in general. It includes a comprehensive table of classification and discusses the clinical features and diagnostic criteria for the five major categories of abnormal facial movement: tremor, chorea, tics, myoclonus and dystonia. A brief outline of the management of these conditions is included, which is fortunate because this aspect is not always covered adequately in later chapters. His classification and discussion are generally straightforward, although not all would agree with the unqualified assertion that 'The most common cause of tics is Gilles de la Tourette's syndrome'.

The section on the anatomy of the facial muscles is essential reading for anyone learning the technique of botulinum injection for blepharospasm or hemifacial spasm. Also of practical value is the chapter by Kimura on the theoretical basis and clinical applications of the blink reflex.

Blepharospasm is the subject of no less than 9 of the 40 chapters in the book, and there is inevitably some duplication and even triplication of information here. Those who still regard this as a psychogenic complaint would do well to read the chapter by Mattie Lou Koster on the patients' perspective: this includes excerpts from letters written by patients, including one by a doctor with the condition, which illustrate vividly the plight of the patient with a difficult movement disorder in search of an explanation of the condition and some effective management of its symptoms. Others should perhaps follow the example of these editors and invite their patients to make a contribution to multiauthor reviews of this kind. Various approaches to the treatment of blepharospasm are dealt with by different authors; the chapter on surgical management contains a series of operative photographs which for the uninitiated and faint-hearted might seem more eye-opening than the procedure itself.

The wider problem of oromandibular dystonia with blepharospasm (Meige's syndrome) is also addressed by several authors in a total of 7 chapters. Despite this—and again some duplication of material—the management of this distressing and virtually untreatable condition is not discussed systematically at any one point in the book. Medication is mentioned briefly in the introductory chapter but none of the three contributions in the 'Pharmacology and Management' section includes much practical advice to the nonspecialist neurologist confronted by a patient with this condition.

The same can be said of classical tardive dyskinesia, another common and difficult clinical problem which might lead the general neurologist to refer to this book. The single reference to treatment in the index again goes back to the brief discussion in the introductory chapter. Some further suggestions about the approach to this therapeutic dilemma do appear in a good contribution by Burke and Kang on the rather less common syndrome of tardive dystonia.

The chapter by Digre and Corbett on hemifacial spasm deals well with the problems of differential diagnosis, possible structural causes and approaches to treatment. In particular, the risks and possible complications of microvascular decompressive surgery are put firmly into perspective. There is a nice misprint on this topic elsewhere in the book, where it is stated that 'An experimented surgeon is needed to perform such a highly specialised procedure'. Also recommended is the chapter by Lees on facial mannerisms and tics, a refreshing diversion into some of the nonmedical aspects of facial expression and movement and the strange world of the ticqueur.

The four contributions on botulinum toxin are important, since this is now becoming the treatment of choice for selected patients with torticollis, blepharospasm and hemifacial spasm; and the technique is likely to be applied more widely to other focal dystonias in the future. The account of possible side effects did not include the occurrence of dysphagia in patients injected for torticollis, which certainly can be a transient problem and in the short term a limiting factor to further injections.

In summary, with the few reservations about duplication of information and the rather patchy discussion of the management of certain disorders, this is a valuable and well-balanced collection of review articles on a fascinating and often difficult area of neurological practice.

Jeremy Gibbs

Neurology and Neurosurgery Illustrated. By Kenneth W. Lindsay, Ian Bone and Robin Callander. 1987. Pp. 565. Edinburgh: Churchill Livingstone. Price £19.50.

Clinical neurology has always lent itself to diagrammatic representation and over the years many texts have been prepared which introduce the student to the problems of regional diagnosis. These texts are based on arresting clinical illustrations and simple neuroanatomy. From Churchill Livingstone we now have a more comprehensive visual representation of the subject prepared by a neurosurgeon, Kenneth Lindsay, from the Royal Free Hospital (when the book was written), and Ian Bone, neurologist, from Glasgow. Robin Callander has prepared the illustrations.

The book is presented in soft back and runs to 543 pages of text and is very competitively priced at just under £20. The authors suggest that the first part of the book emphasizes a method of approaching clinical problems. The second part of the book concentrates on the clinical presentation and management of specific neurological disorders.

The book opens with an illustration of the various technical exercises undertaken to examine the nervous system. Perhaps here a little more detail and accuracy is required. According to the author, testing the visual fields by confrontation is possible provided the examiner has an arm which measures one metre from shoulder to wrist joint. There is a rather simple introduction to the values of plain radiographs, CT, radioisotope scanning and invasive angiography together with NMR and PET. The EEG is dealt with on one side of one page, angiography on two pages with NMR on one page. I feel that the initial two chapters are inadequate and should be revised.

However, the book is valuable in the clinical sections where diagrammatic illustrations of, for example, raised intracranial pressure, give a clear indication of its problems. There is a useful section on coma and impaired consciousness and a usefully illustrated account of the epilepsies. The authors consider symptomatically speech disorders, visual impairment, disorders of the pupil and ocular movement and here the diagrams certainly enhance the text.

Section 4 of the book is devoted to the localization of neurological disease and its management and here, through head injury, vascular disease and tumours, most of the clinical syndromes are illustrated and discussed. The diagrams certainly will provide a useful aid to the student recalling the subject matter of the text. I can detect no significant omissions in this particular section nor indeed in the later section on peripheral nerve and muscle.

There will be many who on seeing this book will discard it as a somewhat naïve and artificial explanation of the complexities of clinical neurology but I feel that for the student entering the neurological clinic and neurological wards for the first time, this will be, by way of introduction, a most useful book and, rather than an adjunct to his more specialized and advanced reading, it will provide a comprehensive and memorable introduction to the subject. I think this book deserves to succeed and where student time is being eroded by so many aspects of the medical curriculum, this readily assimilable survey of neurology and neurosurgery will be very attractive. For postgraduate reading for higher examinations the book is inadequate but again, if the postgraduate student's training has been in fields other than neurology, a night or two with this volume will improve his understanding of the more comprehensive texts.

Finally, I think the book will have a place on the shelves of Departments of Physiotherapy, Occupational Therapy, Speech Therapy and Neuroradiology where a quick reference by the junior members of the departments may explain simply and visually an immediate problem in their own paramedical domain.

J. B. Foster

Tuberculous Meningitis, Tuberculomas and Spinal Tuberculosis. (Second edition.) By Malcolm Parsons. 1988. Pp. 129. Oxford University Press. Price £15.00.

In the ten years or so that have elapsed since the publication of the first edition of this short and handy book, there have been no major therapeutic or diagnostic advances in our knowledge of tuberculosis of the nervous system. However, the addition of almost 100 new references serves to clarify a number of important issues and contributes further to our understanding of the evolution of this illness based on the advances in neuroimaging (water soluble myelography and computerized scanning) to our knowledge of antituberculous drug penetration into the CSF and of the ideal combination of these drugs. Appropriate drug therapy probably depends on relatively ill-understood properties of tubercle bacilli in different stages of activity which may all be present at any one time within the CNS lesions. In particular, this edition deals in more detail with tuberculomas and tuberculous lesions affecting the spinal cord. As before, Parsons reviews the vitally important papers which emerged in the 1950s and 1960s from the Oxford group headed by Honor Smith, and he covers the more recent papers on the pathology and therapeutics from centres of excellence in India, Hongkong and Thailand where most of the current research is being undertaken.

Neurologists on the whole tend to see patients with infections of the nervous system when they present as diagnostic problems, develop unexpected complications or fail to respond to apparently appropriate treatment. If the book can be criticized at all it would be on the grounds that little emerges of Parsons' own personal experiences in recent years in dealing with these problems. Those of us with a special interest in this topic will nevertheless enjoy the book and find the recent references comprehensive; all who have to manage neurological patients in whom tuberculosis comes up as a differential diagnosis will find the book helpful. It is highly recommended.

R. S. Kocen

The Management of Headache. Edited by F. Clifford Rose. 1987. Pp. 192. New York: Raven Press. Price $24.50.

This slim volume is based on lectures given at the Biennial International Symposium organized by the Migraine Trust in 1984. It was designed to be of most practical value to family practitioners and general physicians.

There is some variation in the quality of the chapters; such unevenness often results from multiple authorship with perhaps inevitable repetition and overlap. The book reads enjoyably and the section on systematic classification of headache by Lance is an excellent economical and comprehensive review of the migraine-headache syndromes. Simply written it provides an architecture of the subject which will appeal to the internist as well as the clinical neurologist. Rarer presentations such as retinal migraine and migraine stupor are usefully notated. The remaining companion chapters on clinical features of headache are complementary. I was unconvinced that the subdivision of headache into acute, subacute and chronic, although convenient, represents the best practical neurological approach to subdivision of headache.

Special investigations in migraine indicate that there is no single specific diagnostic test; however, such touchstone precision would only prove helpful in a small, significant group of patients with complicated and atypical migraine or in monitoring treatment. The basic diagnosis is supported in most instances by clinical history and examination.

The chapter on cluster headache by Campbell is a clear practical resumé of this headache syndrome, which is, inexplicably, commonly underdiagnosed. Headache in the emergency department, a nice, wise chapter by Edmeads, should be read with profit by all involved in the diagnosis of difficult headaches. The clinical balance of the chapter is well illustrated by the sentence 'Penalties of the age of neurotechnology are the atrophy of clinical skills and the forgetting that the single best neurological investigation is a repeat history and examination'. Marcia Wilkinson gives a straightforward account of the treatment of the acute attack of migraine, and prophylactic therapy is fully covered by Rose and Peatfield. This last is a useful overview of prophylaxis and experienced clinicians and patients would agree with the conclusion that the drugs of first choice are pizotifen and propranolol. The three chapters on treatment are a detailed account of the therapeutic library and confirm that there is no universally or singular satisfactory prophylaxis or symptomatic treatment for migraine.

The role of abnormal platelet function in aetiology leaves the question open as to whether the behaviour of platelets in regard to 5HT function is a primary abnormality or is secondary to other factors. On the evidence, the conclusion that migraine is not a primary platelet disorder is well argued.

Cerebral blood flow studies provide only indirect support of the metabolic changes during an attack of migraine and from the preliminary evaluation of 31-P topical magnetic resonance we can hopefully look forward to new developments in studying ischaemic and metabolic change. Regional cerebral flow studies during classical attacks of migraine, reported by Olesen, show reduction of regional cerebral blood flow during the aura, persisting into the headache phase, which is not specific to separate major intracranial vascular territories. This argues against the concept of vasospasm. Analogy is drawn with the spreading depression of cortical electrical activity, since the regional blood flow studies do show flow reduction starting in the posterior hemisphere and spreading anteriorly, at times to involve the whole hemisphere.

Evidence is presented for separating common and classical migraine and results of vascular and biochemical studies are at variance with the traditional concept of vasoconstriction and dilatation as significant mechanisms in the migraine syndrome.

This is an interesting book to read, it is well referenced and indexed with clear pointers to the future, emphasizing pathophysiology and mechanism of headache. There is a great deal of information which is of value to the internist in medicine, physician and neurologist in training It is reasonably priced and when the book is laid down, the after-image is lighter in tone than the battleship grey covers of the book.

J. R. HERON

Surgery for Cerebrovascular Disease. Edited by Wesley S. Moore. 1988. Pp. 957. Edinburgh: Churchill Livingstone. Price £120.00.

'With more than 90,000 carotid endarterectomies performed in 1984 (in the United States), and conservatively estimating that 30% of these were done in asymptomatic patients, there is reason for concern among the medical community as to the rationale behind surgical intervention' (op. cit., p. 589). Although in both absolute and relative terms, far fewer carotid endarterectomies are carried out in the United Kingdom, there is, nevertheless, as much concern in the British medical community to evaluate the role of vascular surgery within the therapeutic armamentarium for stroke. A major international study, based in Edinburgh, is currently focused on precisely this topic.

At such a time, therefore, this comprehensive text, edited by a notable American vascular surgeon, is of considerable interest. It must be stated at the outset, however, that the reader seeking proof of superior efficacy of operative management over best medical therapy for stroke will fail to find it here. It is a multiauthor work, with chapters by 42 vascular surgeons, 22 neurologists, 8 neurosurgeons, 4 radiologists and a number of others. The book is intended to be comprehensive, covering epidemiology, pathophysiology, risk factors for stroke, invasive and noninvasive diagnostic methods and medical management, as well as a number of extracranial and intracranial vascular procedures, their indications and how to perform them.

The book is written mainly by vascular surgeons and mainly for vascular surgeons. Some ways of measuring cerebral blood flow and brain energy metabolism are described, but the pathophysiology section dwells largely on structural lesions of extracranial arteries, and on thromboembolism in the genesis of focal brain ischaemia. There is scant mention of ischaemic cerebral oedema, or the concepts of different flow thresholds below which cerebral oedma forms, brain electrical activity ceases, potassium leaves and calcium enters the ischaemic neuron or glial cell. There is reference, however, to recent interest in the role of the excitatory neurotransmitter, glutamate, and the NMDA receptor in the genesis of ischaemic brain damage.

In discussing diagnosis, there is extensive coverage of computed tomography, magnetic resonance spectroscopy and imaging, digital subtraction angiography (venous and arterial), brain electrical activity mapping and duplex ultrasound scanning of the extracerebral vessels. It was disappointing therefore to find no mention of transcranial Doppler studies of the velocity profiles of blood flow in the larger intracranial arteries. Intraoperative measurements of cerebral blood flow, EEG and back pressure in the temporarily occluded internal carotid artery are described, but with little indication of the relative precision and repeatability of these measurements, although this information is available in the British literature. One is left without the crucial information as to whether it really is possible to deduce the degree of reduction in nutritional blood flow to the brain from the change in intracarotid pressure when the vessel is occluded proximally It is stated that the only way to be sure of safety is to operate under local anaesthesia, but while this may detect immediate brain ischaemia, it will fail to predict cerebral ischaemia of delayed onset, the form that is most likely to induce a permanent neurological deficit. What seems to be lacking in this work is discussion of the role of postoperative loss of cerebrovascular reactivity to changes in blood pressure, carbon dioxide and oxygen tension in the genesis of postoperative stroke and in the planning of postoperative care. The pioneering work in this area of Murray Harper and his associates is nowhere mentioned.

This book will give the reader a good, up-to-date overview of the American vascular surgeon's approach to the surgical management of occlusive cerebrovascular disease. British neurologists and neurosurgeons will probably not agree with all that is written here, but they will find it worth while to read this book as, in choosing to disagree with some of the expressed views, they will inevitably identify those areas in stroke diagnosis and management worthy of further academic enquiry and research, and this must be beneficial.

J. DOUGLAS MILLER

Methods in Clinical Trials in Neurology: Vascular and Degenerative Brain Diseases. Edited by R. Capildeo and N -J. Orgogozo 1988. Pp. 327. Basingstoke: Macmillan. Price £40.00.

There can be no doubt that the time is right for a book dealing with clinical trial methodology in neurological therapeutics. Neurology is slowly emerging from an era in which it placed greatest emphasis on the diagnostic skills of physicians to one in which increasingly important management and therapeutic opportunities exist. It is of obvious importance that the new generation of neurologists have a firm grounding and understanding of clinical trials, their planning, conduct, evaluation and interpretation. In attempting to produce a book to summarize this area the authors are to be congratulated, although how far they are successful is open to question.

The book is based on a workshop which was held in Aix-en-Provence, although the date of this is not given. The book is divided into two sections, the first dealing with general considerations of epidemiology, clinical trial design, the use and evaluation of end points and rating scales, and the use of diagnostic tests in therapeutic trials. I think there is little doubt that this is the most useful and informative section of the book for the clinical neurologist. The second section contains a number of chapters dealing with specific therapeutic areas. These are limited to migraine, vascular disease, Parkinson's disease and dementia. The format for each is that published clinical trial methodology is reviewed, found wanting, and heavily criticized; recommendations are then made for improved clinical trial methodology. In many respects the clinical emphasis of these chapters complements the theoretical aspects of the first section very well. However, even though the book's title limits itself to vascular and degenerative brain diseases one wonders whether much could not have been added to the scope of the book by inclusion of other significant therapeutic areas. Thus, epilepsy and multiple sclerosis receive no mention at a time when considerable numbers of clinical trials are being undertaken in these areas and where the methodology developed may be highly relevant to other areas of neurological therapeutics.

Inevitably, the quality of chapters in the second section varies very considerably The most useful are those related to vascular disease where expertise in trial design and conduct owes a great deal to the methodology that has been developed in large scale studies of ischaemic heart disease and its treatment. The clinical neurologist should particularly enjoy Professor Warlow's chapter which demonstrates very eloquently the fact that designing a good clinical trial is relatively simple but that carrying it out is something that presents major problems. He emphasizes that a good clinical trial is a constant compromise between clinical science and clinical reality!

Some chapters leave a great deal to be desired, perhaps because in some instances the authors writing them would not appear to have any great experience of conducting large scale trials in the area in which they are writing. In one instance the authors do not appear to have an understanding of the type of clinical trials involved in phases I, II and III of drug development. Certainly, one wonders whether an input from experienced members of the pharmaceutical industry would not have helped this workshop in its deliberations and in the final production of the book. There is, I think, no doubt that clinicians do need to be more aware of the requirements of regulatory authorities for the 'good clinical conduct' and documentation of studies that are undertaken in drug development programmes.

Overall, there is no doubt that this is a useful book for any clinical neurologist contemplating a therapeutic trial in the areas dealt with by the book. However, the reviewer is left with the feeling that there are a number of omissions which could greatly have strengthened the end product.

D. CHADWICK

An Introduction to Neuropathology. By J. Hume Adams and D. I. Graham. 1988. Pp 309. Edinburgh: Churchill Livingstone. Price £29.95.

This textbook of neuropathology is written with the aim of introducing general pathologists and pathologists in training to the morphological diagnosis of diseases in the nervous system. It is well illustrated with a good selection of instructive pictures. The book contains introductory chapters with descriptions of how to handle postmortem brain material and of the basic cellular and histological reactions of the nervous system to pathological stimuli. These are followed by chapters describing the morphological alterations in different diseases. It also contains very precise and instructive chapters on diseases of muscle and peripheral nerves, written by D. G. F. Harriman.

The book fulfils its aims admirably and it is also of interest for more experienced neuropathologists to share a well written and knowledgeable overview of the topic. Although its focus is on descriptive morphology, it is likely that it will be of interest for clinical neurologists, since there are no other textbooks of this size written in an easily accessible style. There is a tendency nowadays for neuropathology to rely heavily on the classical morphological techniques, which have been so fruitful in the past Modern techniques are not developed or introduced fast enough into neuropathological laboratories From this follows that other neuroscientists (neurobiologists, neurochemists and neuropharmacologists) are now examining pathological material extensively and sometimes this is done without proper contact with or knowledge of elementary neuropathology. For such researchers a book of the present type may also prove to be of value.

KRISTER KRISTENSSON

Magnetic Resonance Imaging. Basis for Interpretation. By Robert Sigal, D. Doyan, Ph. Halimi and H. Atlan 1988. Pp. 102. Berlin: Springer. Price DM 64.00.

This is a really good brief introduction to clinical magnetic resonance imaging (MRI). The book does not confine itself to imaging of the nervous system but there is a strong emphasis on this field. The book attempts to clarify the physical principles underlying the technique and to enable the reader to make a reasoned interpretation of an MR examination instead of extrapolating from previous experience of x-ray CT scanning.

The authors discuss the MRI parameters of a tissue which are of importance in determining the signal produced from a given region and go on to demonstrate how differences in these parameters allow a distinction to be made between tissues, both normal and pathological. The pulse sequences, the various data acquisition parameters, are explained, and the ways in which the pulse sequences are manipulated to exploit differences in the tissue parameters are explored. By understanding in broad terms the effect of a given pulse sequence on the relative signal intensity from different tissues, MRI loses its mystery. Phenomena such as lesions appearing white with one sequence, apparently disappearing altogether with the next sequence and finally appearing as a black area with another sequence, then start to become comprehensive.

As a test to see if the reader has absorbed any of the physics, there then follow pages of MRI exercises, with clinical problems and accompanying images. Just when you thought you understood it all and felt it was again safe to look at MR images!

IAN E. C. ORMEROD

Impact of Functional Imaging in Neurology and Psychiatry. *Current Problems in Neurology 5.* Edited by J. Wade, S. Knezevic, V. A. Maximilian, Z. Mubrin and I. Prohovnik. 1987. Pp. 199. London: John Libbey. Price £26.00.

This is another volume in the increasingly popular John Libbey texts of *Current Problems in Neurology*, which concentrate on neuroimaging and cerebrovascular disease. It relates the proceedings of a meeting held in Yugoslavia in 1986 to assess the impact of functional imaging in the neurosciences. It brought together workers from a number of groups using classical methods of measuring cerebral blood flow as well as more modern techniques using single photon and positron emission tomography. The scope of the meeting extended from diagnostic studies in diseases such as Alzheimer's dementia, to the assessment of abnormal functioning in the brain, for example in the epilepsies, and as a result of remote effects of stroke. The contents page gives a flavour of the rather catholic remit of the meeting, which could be considered both a strength or a weakness of the volume.

The chapters are largely in the form of reviews, though occasionally new data are presented. The standard of image reproduction is patchy with the black and white images frequently leaving much to be desired. There is a reasonable introduction to stable xenon blood flow imaging using computerized axial tomography from Philadelphia, which critically presents limitations and problems with the use of this technique in clinical practice. The conclusion that xenon CT flow information appears to be clinically useful in the diagnosis and management of a broad spectrum of clinical disorders is, however, hardly sustained. Dr Petersen's introduction to the potential role of NMR in measuring or imaging flow, perfusion and diffusion is slightly out-of-date in that substantial advances have been made in this field in the last year (notably by the group of Le Bihar in Paris). Dr Risberg continues to develop xenon rCBF measurements at high resolution using nontomographic detection. It does seem, however, that the field is moving rapidly away from measurement of blood flow as a single parameter and towards the increased sensitivity with depth afforded by tomography. The chapter by Lassen, however, is somewhat disappointing in that the images presented appear to have extremely low resolution, except when the new tracer, 99mm-technetium-HMPAO (Ceretec) is being used. The discussion of CBF tomography with gamma radioisotopes by these authors is a little superficial but is supplemented by a chapter from Ell, which provides more information but also images which at times are hardly convincing. For example, fig. 14 on p. 61, purporting to show a chronic subdural haematoma using 99m-technetium-HMPAO, is singularly unimpressive. Dr Wise's chapter on positron emission tomography is a short but very reasonable introduction and is characterized by a reasonable bibliography for those wishing to acquaint themselves with a variety of studies carried out with this somewhat less accessible technique. Dr Baron produces a short resumé on a subject of considerable interest to his group, that of the remote effects of lesions in the central nervous system. This chapter is unfortunately the most dated but largely because of the advances that have occurred since the meeting took place. There follow a number of chapters largely confined to measurement of cerebral blood flow in a variety of clinical conditions. The vexed question of the pathogenesis and significance of the various blood flow changes seen in migraine is explored by Lauritzen. It can be said that the subject continues to be in a state of flux. Prohovnik attempts to make a case for using cerebral blood flow as a way of diagnosing Alzheimer's disease in life and certainly puts together a considerable amount of data from various imaging techniques suggesting that this clinical possibility may not be too far away.

In summary, however, the volume is somewhat disappointing, as are most collections of papers presented at meetings. The tyro needs a more systematic presentation of facts and the specialist is more likely to go to original papers or more rigorously structured texts. Nevertheless, as a succinct overview to those wishing to get a flavour of the direction in which functional neuroimaging is going this volume may have some appeal. It is also reasonably priced.

R. S. J. FRACKOWIAK

Cranial Magnetic Resonance Imaging. First edition. By A. D. Elster. 1988. Pp. 423. Edinburgh: Churchill Livingstone. Price £75.00.

This book is written by a neuroradiologist for an unspecified readership but it is obviously most suited to neuroradiologists in training and general radiologists with a commitment to magnetic resonance imaging (MRI). A much simplified account of the relevant physics is, nevertheless, at a level which allows a good understanding of the principles and applications of magnetic resonance and of the benefits of the various pulse sequences and parameters. The anatomy is demonstrated on MRI sections of normal mature brain and maturing infant brain; anatomical variants are included and there are sections on the orbit and skull base. It is described in very adequate detail but is supplemented by an excellent multiplanar atlas in which high resolution MR scans are comprehensively labelled.

Individual chapters are devoted to the various types of pathological processes which affect the brain, the supporting and vascular structures, the skull base and the orbit. The clinical and pathological features of each disease are briefly described and the abnormalities which may be found on various diagnostic tests, including other radiological examinations, are discussed, as well as the MRI findings. This approach is very suitable for trainee radiologists, but some other neuroscientists may find the background information unnecessary and be disappointed by the relatively small fraction of the text in some chapters which is actually devoted to MR appearances.

The book is well illustrated with good MR images. Occasional comparison with CT is helpful in defining the supplementary role of the two technologies which the author frequently mentions. A glossary of terms and a section dealing with protocols suitable for particular clinical problems are useful appendages. There is a good index and the references are well selected and extend into 1987.

The book is laid out well and logically produced. One or two obvious misprints do not detract from the text, which is free of controversial features. It is recommended to neuroscientists wishing to acquire a knowledge of MRI but particularly to radiologists and neuroradiologists in training.

BRIAN KENDALL

Applied Neurophysiology. By J. A. Simpson and W. Fitch. 1988. Pp. 358. London: Butterworth. Price £35.00.

There are two factors which may cause this book to sell well: it is printed clearly on white paper of reasonable quality, and it is written by two well-known medical personalities. In some places the text is quite good, as in the descriptions of the autonomic nervous system and cerebral circulation. However, there are other sections where both the text and figures fail to live up to their initial promise. The problem can be traced to the preface. Despite the absence of any indication to the contrary on the front cover, the book is designed specifically for anaesthetists, and the authors believe that anaesthetists, in particular, need to realize that all parts of the brain are interconnected. They wish to emphasize the 'distributed nature of functional systems and their integration'; they wish to paint Sherrington's enchanted loom in its full glory. To emphasize how complicated the nervous system is, we find, in many of the chapters that follow, a good deal of 'integrating' going on in 'diffuse', 'distributed' systems, with particular 'spatiotemporal patterns' and 'multimodal linkages'. We learn that in order to move, 'the computing function requires the integrating properties of polysynaptic convergent neuronal systems'. Similarly, when the cerebellum is destroyed, the 'cross-modal linkages and inhibition/facilitation functions of the cerebral cortex and bulbospinal systems are sufficient to provide almost complete compensation'. Such meaningless strings of words are more usually associated with the sun-kissed campuses of California rather than the dour universities of Scotland.

There are several cases in which the figures do little to clarify the text. This is a shame since most are newly drawn for this book. However, the intention seems to have been to show how complicated the nervous system is, rather than the opposite. Fig. 4.3 is a good example to take since the authors themselves write that it 'shows a complexity beyond comprehension'. Unfortunately, it is not only complex, but misleading, or even wrong. Axons of cells in the cerebral motor areas seem to fuse and form the pyramidal tract. They then bifurcate in the dorsal columns and terminate bilaterally in the spinal cord. There is also an interesting fusion of a pyramidal tract axon with the axon of a cell in the paramedian pontine reticular formation. The descending nonpyramidal pathway lies ventrally in the cord and its bold dotted line ends in a no-man's land above the pons. There are large bold arrows within the cerebellum coming from and leading to nowhere . . . and much more. This is not an isolated example. In fig. 18.1, the medial vestibulospinal tract has its origin in Cajal's nucleus; in fig. 22.1, cortical areas 7, 3, 4 and 6 are arranged lateral to medial on a coronal section of the brain; in fig. 16.1, a K-complex in a 'monopolar' recording (the reference electrode is not specified) looks suspiciously like a blink artefact; and so on.

Even if the book is intended for anaesthetists, I see no reason why they should get a raw deal on their physiology.

John Rothwell

Frontiers in Neuroendocrinology, Volume 10. Edited by Luciano Martini and William F. Ganong. 1988. Pp. 357. New York: Raven Press. Price $150.00.

The latest volume of this outstanding biennial series focuses on four areas of contemporary neuroendocrine research, namely the distribution and function of peptides in central and peripheral tissues, the discovery of new hormones, hormones and development, and clinical neuroendocrinology.

In the opening chapter, Palkovits summarizes in a concise tabular form the wealth of knowledge derived from studies involving immunocytochemistry and biochemical mapping techniques of the topographical distribution of peptides in the brain. Subsequent chapters reflect the impact of molecular biology in this area. Convincing evidence of gene expression of atrial natriuretic factor (ANF), components of the renin-angiotensin system, the neurohypophysial hormones and pro-opiomelanocortin in various central and peripheral tissues is presented. Attention is also focused on the putative roles of these ubiquitous peptides as paracrine, autocrine and endocrine agents with particular emphasis being placed on the intriguing possibility that, in the case of ANF and the components of the renin-angiotensin system, there may be some degree of concordance between the peripheral hormonal and central neuromodulator functions of the peptides.

Novel peptides form the subject of the next two articles. The isolation, characterization and physiology of inhibin and related peptides is eloquently reviewed by Ying while Nikoliks and his colleagues describe the chemistry of the recently discovered gonadotrophin releasing hormone associated peptide (GAP) and debate its controversial role in the regulation of prolactin secretion.

Two fascinating chapters are devoted to developmental neurobiology, a subject which is attracting the interests of many endocrinologists. The first (Arnold and Jordan) deals with the effects of gonadal steroids on the various cellular processes (e.g., synaptogenesis, nerve migration, cell death) which contribute to the structural organization of neural circuits concerned with sexual differentiation and reproductive function. The second (Plant) is devoted to the mysteries of puberty and examines critically the putative mechanisms whereby the dormant GnRH pulse generator may be reactivated in the pubertal monkey.

The final chapters are concerned with the application of knowledge derived from scientific studies to the treatment of disease. Marshall, Monroe and Jaffe discuss the use of LHRH and its analogues in the control of a variety of reproductive disorders while Vance and Thorner examine the interplay of growth hormone releasing hormone and somatostatin in the regulation of somatotroph function and explore the possibility of utilizing the releasing factor as a therapeutic agent in growth hormone deficient children.

This anthology of stimulating review articles is essential reading for scientists and clinicians interested in the complex interplay between the endocrine and nervous systems. The comprehensive and readable nature of the chapters should also make it a useful text for undergraduate students, their teachers and others with a general interest in neuroendocrinology.

Julia C. Buckingham

Introduction to the Anatomy and Physiology of the Nervous System. Fifth edition. By David Bowsher. 1988. Pp. 194. Oxford: Blackwell Scientific Publications. Price £8.95.

This is one of an ever-increasing number of textbooks which aim to reduce the complexities of the nervous system to a level comprehensible to students working within the constraints of modern, compressed medical courses, in which nonclinical and clinical material are integrated to varying degrees.

As with most books of its kind, the early chapters are introductory and are concerned with the basic microscopic and macroscopic structure of the CNS and its surroundings, as well as with aspects of its function. The remainder cover the various systems of the spinal cord and brain. These deal mostly with structure. However, where function is included it is very successfully woven into the fabric of the text, a feature which is conspicuously lacking in many competing publications. Only small amounts of clinical material are included, compared with many of the other textbooks of similar size aimed at the same cohort of students.

In general, the text avoids unnecessary detail and gives a well written and coherent overview of the essentials of each topic by emphasizing unifying features. A good example of this is provided by the chapter on the specific sensory systems. In this, and somewhat unusually, the somatic, visual and auditory pathways are all dealt with together. Themes common to the various pathways are emphasized in such a way as to facilitate learning of the material. In this respect the book succeeds well in comparison with its competitors, many of which bombard the student with highly concentrated and rather fragmented detail. Though the author's individual approach is generally successful, in some instances it may cause difficulties for a student consulting other textbooks, as for example in relation to the interpretation of the terms *myelinated* and *unmyelinated* in Chapter 2.

The general approach adopted by the author is most suited to bringing together material already covered in lectures and practical classes. This also applies particularly to the illustrations which are mainly in the form of radically simplified diagrams. The most useful illustrations are the relatively detailed schematic diagrams showing the connections of each of the main systems. These largely replace the conventional wiring diagrams showing fibre pathways superimposed on profiles of appropriate parts of the CNS.

This book is satisfactorily produced for its cost, though some of the diagrams lack crispness. However, the number of printing errors is rather high, considering that this is the fifth edition.

Many recent textbooks have responded to the current massive increase in knowledge of CNS structure by including more detail than the average medical student can cope with in the time available. This book has avoided that pitfall. It remains very useful as an adjunct rather than an introduction to undergraduate studies of nervous system structure.

JOHN P. FRAHER

The Paraneuron. By T. Fujita, T Kanno and S. Kobayashi. 1988. Pp. 367. Tokyo and London: Springer. Price DM 348.00.

The paraneuron concept was first introduced by Tsuneo Fujita and Shigeru Kobayashi in 1975–6 for cells then designated as 'endocrine brothers of neurons'. The concept differs from the APUD concept of Professor Tony Pearse, which identifies cells capable of amine-precursor uptake and decarboxylation, in that it designates cells as paraneurons if they (1) produce substances identical with or related to neurotransmitters or neurohormones, (2) possess neurosecretory-like and/or synaptic-type vesicles or granules, and (3) have receptosensory function.

Clearly the two concepts overlap in terms of cells included and initially both incorporated a belief that APUD cells and paraneurons are neuroectodermal in origin. However, recent experimental embryological work, particularly by Nicole Le Douarin and her colleagues, has shown that this is not so and that structures designated as APUD cells share common functional and histochemical characteristics while those designated paraneurons share common structural and functional characteristics and usually an intimate association with neurons (usually terminals of axons or dendrites).

Following a general introduction, the authors consider in detail nineteen cell types designated as paraneurons which range from chromaffin and gastroenteropancreatic hormone-producing cells to

Merkel cells of the skin, visual cells of the retina and mast cells. In respect to each cell type phylogeny, ontogeny, distribution, cytochemistry, cell kinetics, secretory activity and function are considered and a chapter is devoted to protein cell markers and tumours of paraneurons (paraneuromas).

This is an interesting and stimulating concept which stresses the need to take account of structural and specific functional similarities in cells as well as, or in some cases instead of, ontogeny, in considering their biological role and pathology. It may offend those traditionally trained to link the embryological origin of cells with function and pathology.

The book is very well presented and illustrated and the occasional typographic error and Japanese-English syntax are readily ignored due to the clarity and excellence of the sequential presentation of the subject matter. For those interested in the fundamental and applied aspect of neurobiology it can be read through and enjoyed in the same way as a biography and subsequently returned to for special reference. The timing of its publication is opportune, especially in light of the recent evidence being presented for the possible secretory role of sensory neurons I have no hesitation in recommending it to honours students and postgraduates working in the field of neurobiology, and to neuropathologists and clinicians interested in fundamental as well as applied neuroscience and endocrinology.

R E. COUPLAND

ANNOUNCEMENTS

Fyssen Foundation 1989 International Prize

The general aim is 'to encourage all forms of scientific enquiry into cognitive mechanisms, including thought and reasoning, underlying animal and human behaviour, into their biological and cultural bases, and into their phylogenetic and ontogenetic development'. For this purpose a substantial *International Scientific Prize* will be awarded for a major contribution to the progress of knowledge in the fields of research supported by the Foundation such as ethology, palaeontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences. The discipline for the 1989 Prize is Neurosciences.

Nominations for the 1989 Prize should be sent (15 copies) to the Secretariat of the Foundation, 194 rue de Rivoli, 75001 Paris, and should include a curriculum vitae of the nominee, a list of his publications and a summary (4 pages maximum) of the research upon which the nomination is based

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Completed applications (15 copies) should be sent to the Secretariat of the Foundation, 194 rue de Rivoli, 75001 Paris Applications must be received by March 31, 1989.

XXXI International Congress of Physiological Sciences

This congress will be held in Helsinki, Finland, on July 9–14, 1989. This is the centennial congress, the first having been held in Basel, Switzerland, in 1889 The Final Announcement, registration and abstract forms may be obtained from the Secretariat, XXXI International Congress of Physiological Sciences, PO Box 722, SF-00101, Helsinki, Finland Telex 122529 trex sf

Molecular Aspects of Diseases of Motor Function

Organized by the Neurochemical Group of the Biochemical Society, this meeting will be held at Royal Holloway and Bedford College, London on March 30-31, 1989. The programme will include neuromuscular disorders, neurovirology and neurological syndromes, and movement disorders. For further details contact Dr A J. Cross, Astra Neuroscience Research Unit, 1 Wakefield Street, London WC1N 1PJ.

19th Central European Neurological Symposium

This will be held in Vienna, Austria, at the Palais Auersperg on June 29-July 1 1989. The main topics will be clinical imaging and metabolic aspects of age-associated and degenerative neurological diseases. Further information may be obtained from Mrs Elisabeth Ribar-Maurer, Wiener Medizinische Akademie, Alser Strasse 4, A-1090 Wien, Austria (tel. (222) 4213 83-0, Fax (222) 42 1383-23). The deadline for submission of abstracts is March 31, 1989.

Princeton Drug Research Symposium

A symposium on current and future trends in anticonvulsant, anxiety and stroke therapy will be held at the Hyatt Regency Hotel, Princeton, New Jersey, USA, on May 21-23, 1989. Further information may be obtained from Dr J. Emmett, The Studio, 12 High Street, Wheathampstead, Herts AL4 8AA, UK (tel. 058-283-4117).

Canadian Congress of Neurological Sciences

This will be held in Ottawa on June 14–16 1989. Further details may be obtained from the Secretariat, Canadian Congress of Neurological Sciences, 116C, 1330-15 Ave SW, Calgary, AB Canada T3C 3N6.

Tissue Culture in Neurobiology

An 8 day intensive residential course on this topic intended for scientists and senior graduate students will be held in Saskatoon, Saskatchewan, Canada, on May 4–12 1989. Registration fee $250. Enquiries and applications should be made to Dr S Fedoroff, Department of Anatomy, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N CWO, Canada.

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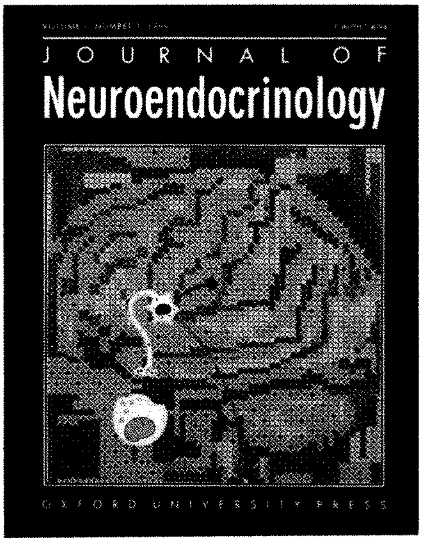

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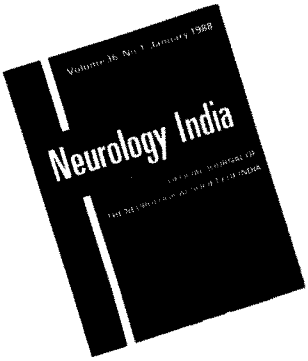
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SPATIOTEMPORAL CONTRAST SENSITIVITY AND COLOUR VISION IN MULTIPLE SCLEROSIS

by DAVID TRAVIS[1] *and* PETER THOMPSON

(From the Department of Psychology, University of York, Heslington, York, UK)

SUMMARY

Measures of contrast sensitivity and colour vision were taken from a group of 18 multiple sclerosis patients. Contrast sensitivity losses, measured at 5 spatial frequencies and 4 temporal frequencies, were found to be significant in 11 patients. Red/green (Rayleigh equation) and green/blue (Engelking-Trendelenburg equation) Pickford-Nicolson anomaloscope settings were abnormal in 15 patients. Correlating each of the 20 spatiotemporal losses with the colour losses revealed that in 19 conditions the red/green loss was greater than the green/blue loss. None of the green/blue losses correlated significantly with spatiotemporal losses while between 2 and 8 cycles/deg 11/12 spatiotemporal conditions showed significant correlations with red/green colour loss. These results support a locus of damage before the cortex at a stage in the visual pathway where red/green chromatic information may be encoded in pathways which also code luminance information.

INTRODUCTION

The visual pathway is particularly susceptible to damage in multiple sclerosis (MS). Magnetic resonance imaging (MRI) has revealed damage to the optic tract in some patients (Rosenblatt *et al.*, 1987) and damage to the optic radiations in about two-thirds of patients presenting with a common precursor of MS, optic neuritis (W. I. McDonald, personal communication). Clearly, lesions to the optic nerve, tract and radiations are frequent in this disease. It is precisely these precortical pathways that have been the focus of recent advances in our understanding of the neurophysiology of vision. The convergence of many receptor cells onto relatively few ganglion cells demands an efficient code of information processing along the visual pathway to the visual cortex. Accumulating evidence (Wiesel and Hubel, 1966; De Valois *et al.*, 1977; Ingling and Martinez 1983; Ingling and Martinez-Uriegas, 1985; Derrington *et al.*, 1984) suggests that, within this information processing 'bottle-neck', many parvocellular cells in the lateral geniculate nucleus (LGN) may be transmitting information both about the colour and the luminance of a stimulus: they are performing a 'double-duty'.

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This general view is far from proven. While all experimenters appear to agree that the parvocellular cells, with their overt chromatic opponency, are vital for colour processing, their role in mediating achromatic contrast sensitivity is less well established. The magnocellular pathway, with substantially higher contrast sensitivity, appears to be the better candidate. However, the receptive fields of the cells of this pathway are large and they represent perhaps only 10% of the cells covering the fovea. High contrast sensitivity therefore seems to be combined with poor spatial resolution. Shapley and Perry (1986) claimed that the contrast sensitivity function may reflect the activity of the magnocellular pathway at all but the higher spatial frequencies, but Derrington and Lennie (1984) pointed out that probability summation between as few as 10 parvocellular cells would be needed to regard the contrast sensitivity function as a reflection of the parvocellular pathway. Certainly selective destruction of the parvocellular pathway by acrylamide (Merrigan and Eskin, 1986) does reduce contrast sensitivity by almost a factor of ten.

This debate will doubtless develop in the future. Its relevance for clinical investigations of visual perception in MS is unquestionable; already it has required us to treat studies which have regarded the physiological damage in this disorder in terms of selective loss to X or Y pathways with some caution. Considering these advances, psychophysical tests designed to identify more precisely the site of damage in the visual pathways in MS are of the utmost importance.

Traditionally, psychophysical investigations of the visual losses seen in MS have concentrated on contrast sensitivity or colour vision. The contrast sensitivity deficit for stationary gratings appears to take one of four forms: the contrast sensitivity function may show an overall depression; or the loss may be restricted to gratings of low, medium or high spatial frequencies only (Regan *et al.*, 1977; Frisén and Sjöstrand, 1978; Bodis-Wollner *et al.*, 1979; Zimmern *et al.*, 1979; Hess and Plant, 1986). When gratings are temporally modulated (either drifted at constant velocity or phase alternated) a different picture emerges. Some authors (Brussell *et al.*, 1984) have claimed that the deficit observed for stationary gratings persists unchanged into the temporal domain; others (Plant and Hess, 1985) have argued that the loss of sensitivity decreases at high rates of movement but for gratings of low spatial frequency only; still others (Medjbeur and Tulunay-Keesey, 1985) have found that temporal modulation can increase or decrease the deficit for stationary gratings or interact with spatial frequency and reverse the pattern of results found with stationary gratings. These authors have often interpreted their results within a psychophysical model that proposes channels tuned to some range of spatial and temporal frequencies (Watson and Robson, 1981; Thompson, 1984; Hess and Plant, 1985). However, this approach does not enable the identification of the site of any lesion because spatial and temporal frequency tuning is present at the level of the ganglion cells (Enroth-Cugell and Robson, 1966) as well as in the visual cortex (De Valois *et al.*, 1982).

Ostensibly, colour vision testing offers a more secure method of identifying the site of the lesion in MS. Work by a number of researchers (*see* Pokorny *et al.*, 1979, for a review) permits the identification of the site of physiological damage associated with discrete acquired colour vision deficits, at least distinguishing between receptoral, postreceptoral and cortical locations. Kollner's Rule, for example, states that blue defects are characteristic of retinal disorders and red-green defects of optic nerve disorders. However, the nature of the colour vision deficit in MS has proved elusive. Most workers would agree that, when examined with conventional tests of colour vision, the defect resembles that found in acquired, rather than congenital defects; but the errors may be difficult to specify (Griffen and Wray, 1978), or be confined to a red/green (e.g., Cox, 1961) or 'blue/yellow' (e.g., Ohta, 1970) dimension. In general terms, these correspond to the type II and type III acquired colour vision deficits classified by Verriest (1963). In type II loss discrimination along a red-green axis deteriorates progressively with a concomitant milder blue-yellow loss. The more common type III loss is characterized by a mild or moderate loss of discrimination on what is often called the blue-yellow axis. However, it should be noted that a type III tritan-like deficit actually results in blue/green and violet/yellow confusions and not blue/yellow confusions (*see* Wright, 1979).

Using more sophisticated psychophysical procedures, some experimenters have reported that patients with MS exhibit a larger loss of luminance than chromatic function (Zisman *et al.*, 1978; Alvares *et al.*, 1982). However, others (Fallowfield and Krauskopf, 1984; Mullen and Plant, 1986) have reported that the transmission of colour information is more severely impaired. Still others have reported the losses to be nonselective (Foster *et al.*, 1985; Sellers *et al.*, 1986). These results may be in conflict partly because of the not inconsiderable problem of designing experiments that test independently luminance and chromatic functions, and partly because their model of postreceptoral colour processing requires the separation of chromatic and luminance information within the optic nerve.

If some parvocellular cells are multiplexing both luminance and chromatic information, as discussed above, then these dimensions, far from being transmitted along independent pathways, are encoded by a single pathway that performs 'doubly-duty'. Furthermore, certain acquired defects of colour vision that arise from damage to the optic nerve or tract would go hand-in-hand with contrast sensitivity deficits. Specifically, physiological evidence (Derrington and Lennie, 1984; Derrington *et al.*, 1984) shows that the cells in the parvocellular layers of the lateral geniculate nucleus receiving input from long and middle-wave cones (L-M cells) respond well to colour modulation at low spatial frequencies and luminance modulation at high spatial frequencies. One prediction from this is that, as red/green discrimination deteriorates, so too should contrast sensitivity. Note that 'red/green discrimination' is used here to mean a discrimination depending only on activity in L-M cells, such as a discrimination between a pair of protanopic or deuteranopic metamers. The same physiological work has shown that other parvocellular units (those that receive opposed inputs from short-wave cones and some combination of long and middle-wave cones, i.e., S-(L and M) cells) are relatively unimportant for spatial vision. We can therefore predict that a deficit on a similar colour discrimination task depending only on activity in S-(L and M) cells (e.g., a discrimination between two tritanopic metamers) should not correlate with a contrast sensitivity loss.

We have measured contrast sensitivity losses and colour discrimination losses in MS patients to ascertain whether the relationships outlined above occur. If such a relationship were found, it would suggest that, at least in the peripheral visual system where damage is most often reported in MS, the psychophysicists' colour and luminance 'channels' do not have separate neurophysiological underpinnings. Such a result would be of obvious importance in any attempt to build a model of optic nerve damage in this disease.

METHODS

Subjects

The clinical subjects were 18 patients with MS, 4 males and 14 females. The patients were 'clinically definite' cases according to the criteria of Rose *et al.* (1976). None of the patients was in an acute phase of their disease. The age range of the subjects was 33 to 63 yrs with a mean age of 46.1 yrs (±8.9 SD). Informed consent was obtained from all patients. Subjects wore their best optical correction for all experiments.

Control subjects were used in the assessment of colour vision. Two separate control groups were used, drawn from a population of Open University students attending Summer School at the University of York. The control group for the Rayleigh equation (*see* below) consisted of 20 subjects, 9 males and 11 females. The age range of these subjects was 35 to 67 yrs with a mean of 45.8 (±7.5 SD). The control group for the Engelking-Trendelenburg equation also consisted of 9 males and 11 females. The age range of this group was 38 to 59 yrs with a mean of 46.5 (±6.9 SD). In order to facilitate comparison with the MS patients, (1) the control subjects performed the anomaloscope test monocularly, but only one eye was tested (the left eye in all except 1 case); (2) subjects were selected to be within the appropriate age range because of the known effects of age on colour vision (e.g., Verriest, 1963). Before testing, subjects were screened for congenital colour deficiency with the Ishihara test for colour blindness and the Farnsworth F2 tritan plate. Two potential subjects, both male, failed this screening test and were not examined on the anomaloscope. It was necessary to use two separate control groups because demands on the students' time meant they could only participate in one experiment.

Contrast sensitivity measurements

Apparatus and stimuli

Computer-generated vertical sinewave gratings were displayed on the screen of a Joyce Electronics display with P4 phosphor. The frame rate used was 100 Hz. The subject viewed a circular, 1.85° diameter patch of grating. Screen luminance, measured with a Minolta Chromameter CS-100, was 100 cd/m^2. Contrasts in the range 0–77% were used.

Procedure

Subjects sat 298 cm from the screen. Precise viewing distance was controlled with a head rest. Subjects were instructed to maintain fixation on a small high contrast dot in the centre of the screen, and natural pupils were used. Viewing was monocular and each eye was tested in turn. In most of our patients we were able to obtain more than one set of measurements for each eye; when this was the case, the order of testing was good eye, bad eye, bad eye, good eye. The good eye was defined as the eye with the better Snellen acuity. Subjects were rested between each experimental run. The eye not used was occluded with translucent diffusing paper. We chose not to use an eye patch since in preliminary work with some patients we found that this resulted in temporary monocular diplopia in the occluded eye: this could seriously contaminate contrast sensitivity measures (*see* Apkarian *et al.*, 1987; Travis *et al.*, 1987).

We used the Method of Adjustment to collect the threshold measurements since we have found this to be most efficient with our patients' time. One of 20 gratings was selected randomly by the computer. The grating was one of 5 spatial (1, 2, 4, 8 and 16 c/deg) and 4 temporal (0, 1, 4 and 16 Hz) frequencies. The selected grating was then presented to the subject at a contrast of 7.7%. The subject, using a response box, was able to raise or lower the contrast of this grating in 2 dB steps until it was at detection threshold, and this contrast was recorded. Our subjects were instructed to regard threshold as the contrast at which they could just determine that they were not looking at a uniform blank screen. The next grating was then presented according to the predetermined random sequence. When modulated in time, successive gratings were drifted right or left alternately. There was no time limit set for completion of a threshold setting, but subjects were advised not to agonize over their decision. With this method we found that all of our subjects were able to set thresholds with accuracy, repeatability and speed: a complete spatiotemporal contrast sensitivity function could be obtained in under 10 min. In these experiments the temporal modulation of a stimulus involved drifting it at constant velocity.

Colour vision measurements

Apparatus and stimuli

Colour vision was assessed with the Pickford-Nicolson anomaloscope (for full details of this instrument, *see* Pickford and Lakowski, 1960). We chose to use a commercially available instrument rather than a more sophisticated laboratory test in order that our results might be of some clinical usefulness. In this instrument, the subject views a circular translucent panel. The panel is divided such that the hue of the right half (the test field) is provided by the mixture of two primary lights. The hue of the left half (the standard field) is fixed. The coloured lights are produced by passing light from a tungsten source through glass filters. The dependent measures are the range of mixtures of the two primaries in the test field that the subject will accept as a match to the standard field, and the midpoint of this range. These are obtained from the dial setting on the anomaloscope that controls the mixture of the primaries (the dial on the instrument is marked off in arbitrary units from 0–82).

We chose to measure two equations: the Rayleigh equation (i.e., a mixture of red and green to match yellow) and the Engelking-Trendelenburg equation (i.e., a mixture of blue and green to match blue/green). We use the first as an estimate of the red/green colour deficit (i.e., the extent of protanopia or deuteranopia) and the second as an estimate of the blue/green colour deficit (i.e., the extent of tritanopia). Ideally, the primaries in both cases should lie on dichromatic confusion lines so that, for the respective dichromats, the full matching range will be indistinguishable from the standard; in the Pickford-Nicolson anomaloscope the primaries lie close to, but not on, these theoretical confusion lines (*see* Pokorny *et al.*, 1979, pp. 106–110). However, we have confirmed that both kinds of congenital red-green dichromat will accept the full range of red/green mixtures on our instrument; we have so far been unable to test any tritanopes.

Procedure

Subjects sat 1 m from the screen. At this distance, the circular stimulus subtended 1.43° of visual angle. Viewing was monocular, through natural pupils, and both eyes were tested. Fixation was not constrained. The Rayleigh equation was always measured first. Each eye was tested once only on each equation, and the order of the tests was as for contrast sensitivity testing.

The testing procedure was carried out according to the instruction manual (Pickford and Lakowski, 1960). The experimenter first found a mixture of the two primaries in the test field that the subject would accept as a match to the standard; and next explored the end points of this match. The dial readings at these end points were then noted.

RESULTS

Contrast sensitivity measurements

Of the 18 patients, 12 had Snellen acuities of 6/6 or better in both eyes; a further 3 patients had acuities of 6/6 or better in one eye. Only 1 patient had both eyes with worse than 6/9 acuity.

Each patient's contrast sensitivity was measured at 5 spatial frequencies (1, 2, 4, 8 and 16 c/deg) at each of 4 temporal frequencies (0, 1, 4 and 16 Hz). Eleven patients showed a significant loss in one eye compared with the other ($P < 0.05$ on a two-tailed sign test). In the remaining 7 patients there was little to suggest any highly selective loss that might be swamped by analysing all 20 spatiotemporal conditions together. Fig. 1 shows in summary form the better eye on each of the 20 conditions for the 18 patients.

Characterizing the pattern of loss in individual patients is not easy as the data from single patients are not readily evaluated by statistical tests. However, we have

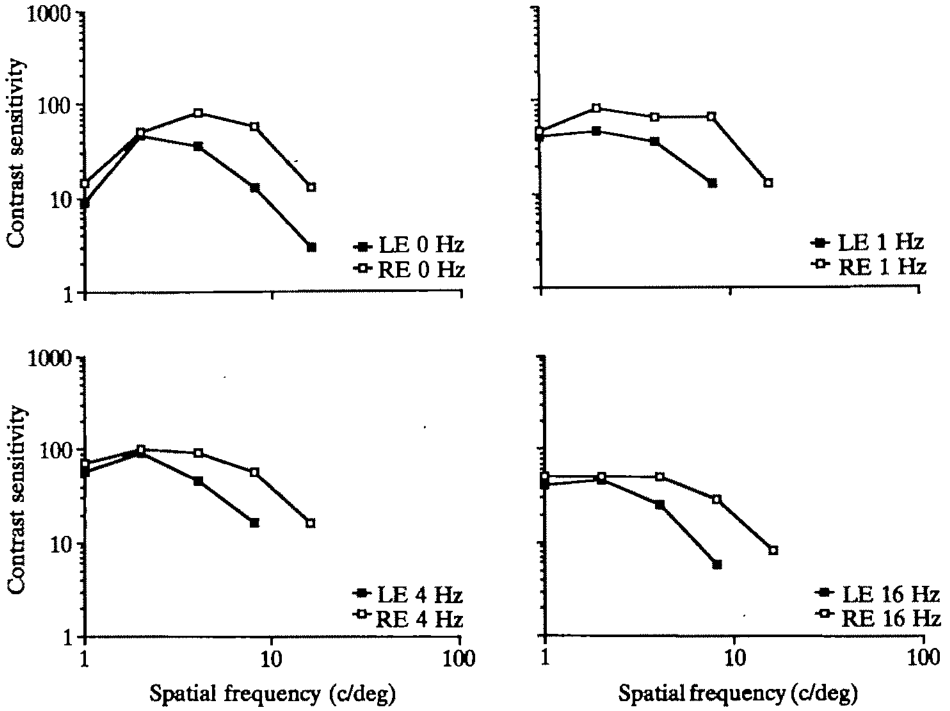

FIG. 1. Contrast sensitivity of *Case 18*. Filled squares show results for this patient's left eye, open squares for the right eye. Sensitivity (i.e. the reciprocal of the contrast, as a percentage, at threshold) is plotted against spatial frequency. Results are plotted separately for the four temporal frequencies.

TABLE 1. SPATIOTEMPORAL MAPS FOR 18 SUBJECTS WITH MS.

	Case 1				*Case 2*				*Case 3*			
	LE 6/5		*RE 6/5*		*LE* $6/5^{-1}$		*RE* $6/6^{-1}$		*LE* $6/5^{-3}$		*RE* $6/6^{-2}$	
16	R	R	R	L	R	R	L	L	L	L	L	
8	L	L	L	L	R	O	O	L	L	L	L	L
4	L	L	L	L	L	L	L	R	L	L	L	L
2	L	L	L	L	R	R	L	L	L	L	L	L
1	L	L	L	L	L	L	L	L	R	L	L	R
	0	1	4	16	0	1	4	16	0	1	4	16
	*Case 4**				*Case 5*				*Case 6*			
	LE 6/5		*RE 6/5*		*LE 6/5*		*RE* $6/5^{-1}$		*LE 6/6*		*RE* $6/6^{+4}$	
16	R	R	R	R	L	L	L	O	L	L	L	
8	L	R	R	R	O	R	O	R	R	R	L	R
4	R	L	R	L	R	O	O	R	R	L	L	L
2	R	R	L	R	R	L	L	R	R	L	O	R
1	L	R	R	R	O	R	R	R	R	R	L	R
	0	1	4	16	0	1	4	16	0	1	4	16
	Case 7				*Case 8**				*Case 9**			
	LE $6/9^{-1}$		*RE* $6/9^{-1}$		*LE* $6/6^{-3}$		*RE* $6/12^{+2}$		*LE* $6/9^{+2}$		*RE* $6/6^{+2}$	
16	L	R	L				L		R	L	R	R
8	R	R	R	L	L	L	L	L	R	R	R	R
4	R	R	R	R	L	L	L	L	O	R	O	R
2	R	L	L	R	L	L	L	L	R	L	R	R
1	R	L	L	R	R	L	L	L	R	R	O	R
	0	1	4	16	0	1	4	16	0	1	4	16

	*Case 10**				*Case 11*				*Case 12*			
	LE $6/12^{-1}$		*RE* $6/6^{+2}$		*LE 6/12*		*RE 6/18*		*LE 6/6*		*RE 6/6*	
16					R	L			R	R	O	R
8	R	R	R	R	L	L	L	L	L	O	R	R
4	O	R	R	R	L	L	L	L	R	O	L	R
2	R	R	R	R	L	L	R	R	R	O	R	O
1	L	L	R	R	L	L	R	R	L	L	R	L
	0	1	4	16	0	1	4	16	0	1	4	16
	*Case 13**				*Case 14**				*Case 15**			
	LE 6/9		*RE* $6/24^{+1}$		*LE 6/5*		*RE 6/5*		*LE 6/6*		*RE 6/5*	
16	L	R	L	L	L	L	R	L	R	R	R	
8	L	L	L	L	L	L	L	L	R	R	R	R
4	L	L	L	L	L	L	L	L	R	R	R	R
2	L	L	R	L	L	L	O	R	L	R	R	L
1	R	R	O	L	L	R	O	O	O	L	L	R
	0	1	4	16	0	1	4	16	0	1	4	16
	Case 16				*Case 17**				*Case 18**			
	LE 6/5		*RE 6/5*		*LE* $6/5^{-2}$		*RE* $6/6^{-3}$		*LE* $6/6^{+2}$		*RE 6/5*	
16	O	L	R		L	L	L	L	R	R	R	R
8	O	R	R	L	L	L	L	L	R	R	R	R
4	L	L	L	O	L	L	L	L	R	R	R	R
2	R	L	R	R	R	L	L	L	R	R	R	R
1	R	L	O	R	L	L	L	L	R	R	R	R
	0	1	4	16	0	1	4	16	0	1	4	16

Shown for each subject is the better eye (L = left, R = right, O = no difference) on the 20 spatiotemporal conditions. Each column corresponds to one of the four temporal frequencies; each row corresponds to one of the five spatial frequencies. For some subjects at the highest frequency, threshold measurements could not be obtained for either eye and hence these cells are left empty. Note that presenting the data in this simplified way conceals information about the magnitude of the difference at the different spatiotemporal points. An asterisk next to a subject number shows that the measured pattern of loss was significantly different from chance ($P < 0.05$).

no evidence for the narrowly-tuned spatial frequency losses reported by some researchers (e.g., Bodis-Wollner and Diamond, 1976; Regan *et al.*, 1981; Medjbeur and Tulunay-Keesey, 1985; Hess and Plant, 1986) and have found no evidence for narrowly-tuned losses in the temporal frequency domain. This latter result is unsurprising as it is now generally acknowledged that at each spatial frequency perhaps just two or three broad-band temporal channels exist (*see* Watson and Robson, 1981; Thompson, 1984; Anderson and Burr, 1985; Hess and Plant, 1985).

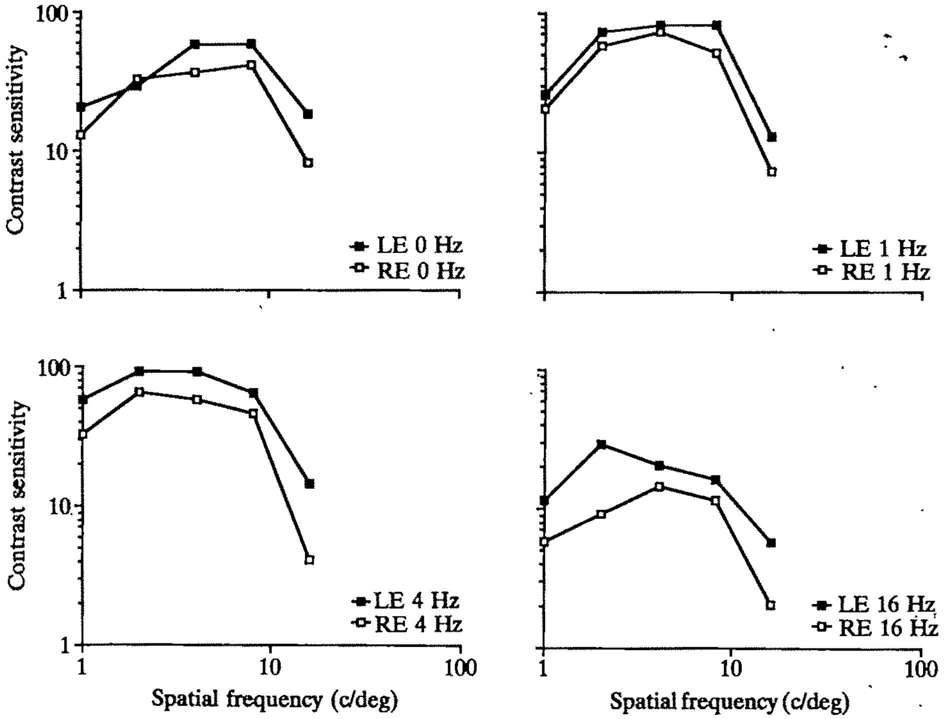

FIG. 2. Contrast sensitivity of *Case 17*. Details as fig. 1.

Of the 11 patients who showed significantly reduced sensitivity in one eye, 3 (Cases 4, 17, 18 in Table 1) appeared to suffer from a general loss at all spatial and temporal frequencies investigated, an example of which is seen in fig. 1. In 1 of these patients the loss appeared to increase quite markedly with increasing temporal frequency (*see* fig. 2). A further 3/11 patients (Cases 3, 8, 15 in Table 1) showed a similar pattern of loss but with little or no low spatial frequency loss.

Four of the 11 patients (Cases 3, 10, 13, 14 in Table 1) showed a different pattern of loss at low temporal frequencies than they did at high temporal frequencies. Fig. 3 illustrates 1 case where the contrast sensitivity loss between the two eyes disappeared with increasing temporal modulation and fig. 4 illustrates a case in which such a loss is revealed more reliably at high temporal frequencies.

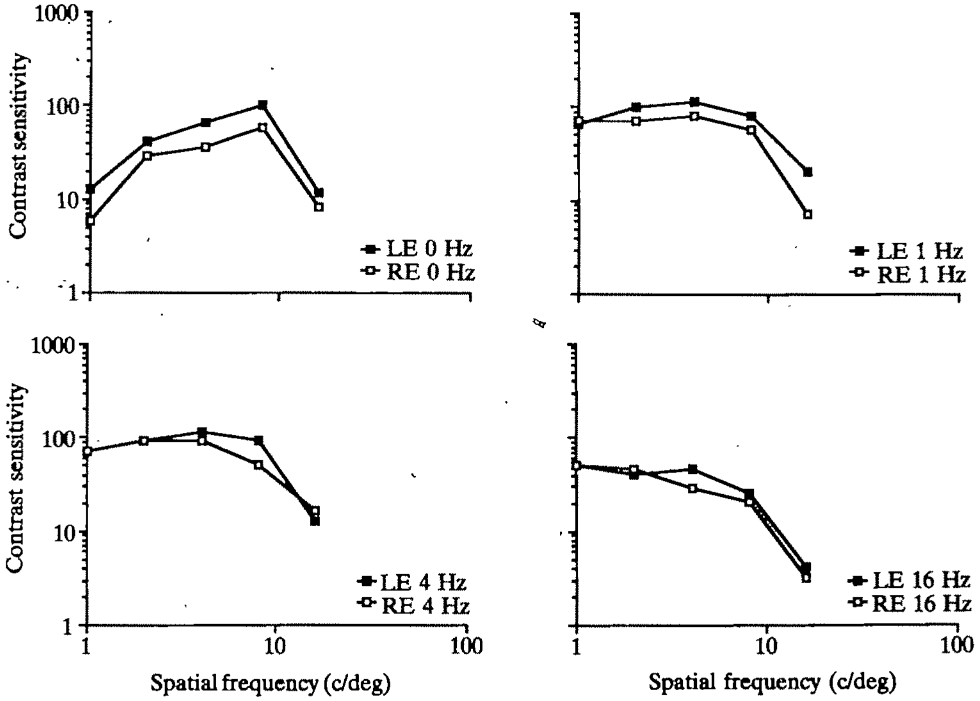

FIG. 3. Contrast sensitivity of *Case 14*. Details as fig. 2.

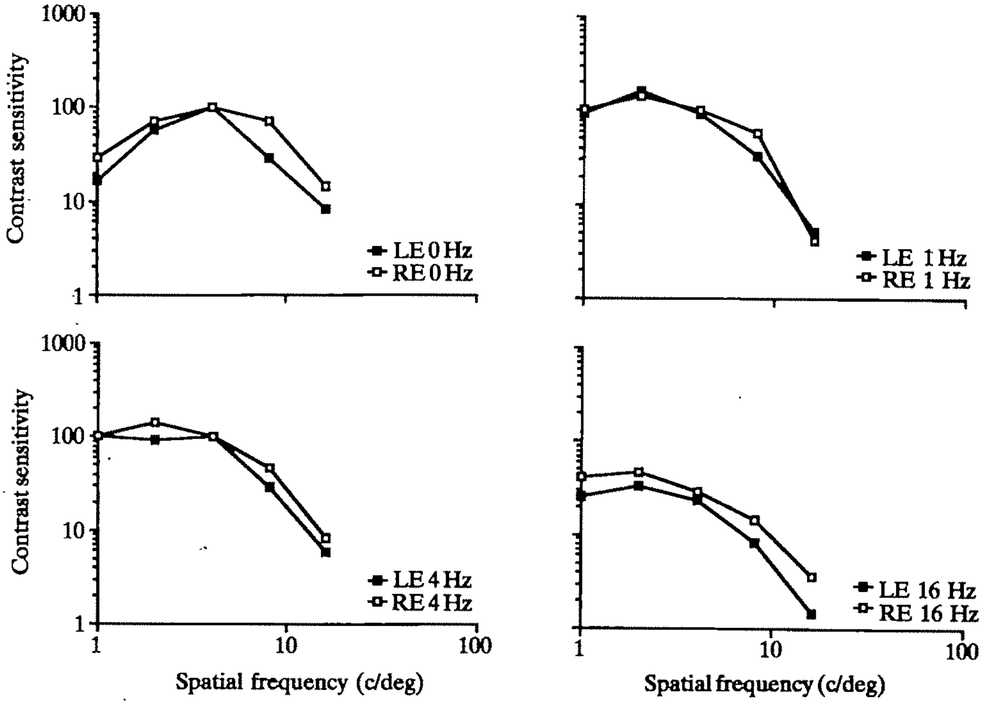

FIG. 4. Contrast sensitivity of *Case 9*. Details as fig. 2.

One patient (Case 1, fig. 1) showed a pattern of loss which deserves particular attention (*see* fig. 5). A small but highly reproducible relative loss in her right eye at low and medium spatial frequencies disappeared at high spatial frequencies where the left eye was less sensitive. This patient reported that the right eye was her 'bad' eye and yet could be shown to have higher acuity with that same eye.

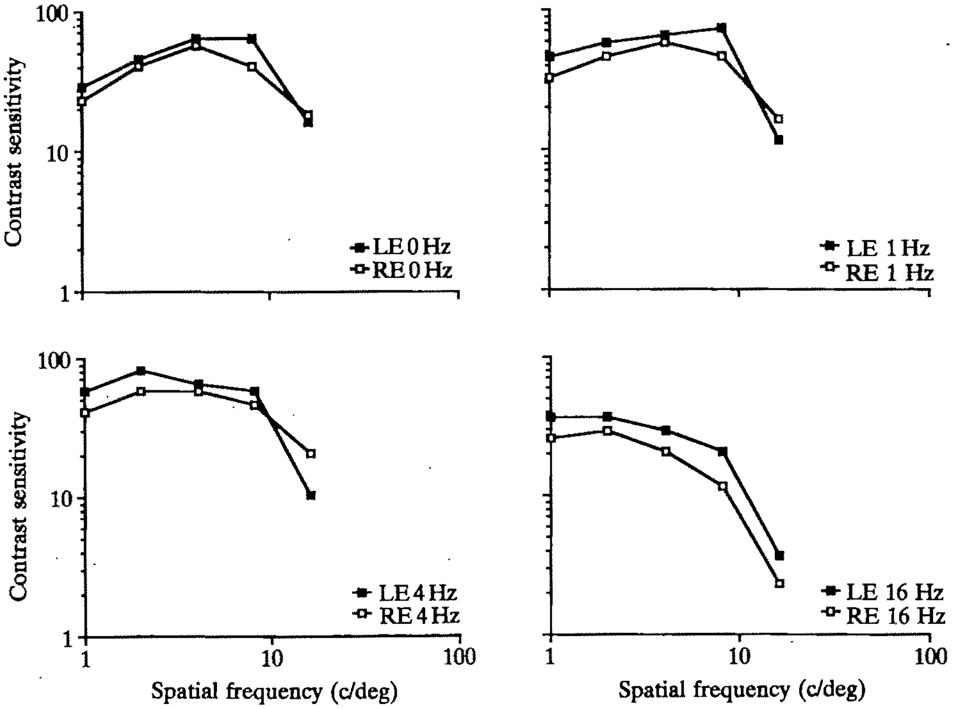

FIG. 5. Contrast sensitivity of *Case 1*. Details as fig. 2.

Colour vision measurements

When taken together, the data for the matching ranges on the Rayleigh and Engelking-Trendelenburg equations classify at least one eye of 15/18 (83%) of the patients as colour weak.

Results for each patient on the Rayleigh (red/green) equation are shown in fig. 6. Data for each eye are plotted separately. Plotted in the fig. is the range of red/green mixtures that the subject would accept as a match to the standard yellow. The larger, open symbol at the top of the fig. shows the mean setting ±2.58 SD (99% confidence limits) for the group of control subjects. The mid-matching point (i.e., the centre of the matching range) for all but 3 patients (5 eyes) falls within 2.58 SD of the mean of the control group.

The subjects (Cases 3, 6, 8) who fell outside these limits were subsequently

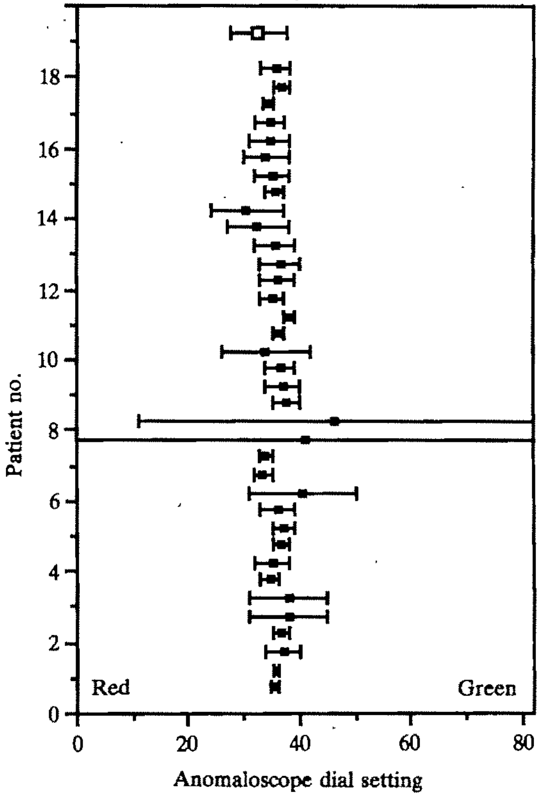

FIG. 6. Matching ranges and mid-matching points on the Rayleigh equation of 18 subjects with MS. The abscissa plots the scale setting of the anomaloscope: a value of 0 represents the most saturated red and 82 the most saturated green that the instrument could produce. Each filled symbol shows the mid-matching point for a particular subject; the associated bars show the range of settings that the subject would accept as a match to the standard yellow. The large open symbol at the top of the fig. shows the mean mid-matching point ±2.58 SD of the control group. Results are shown for both eyes of each subject (the eye order from the bottom of the fig. upwards is right eye, left eye).

tested on the Ishihara test. Case 3 made three errors with her right eye but none with her left eye: given these results and that congenital red/green colour blindness is rare in females, her defect is probably acquired. Case 8, tested binocularly on the Ishihara test, made only one error; Case 6 made many errors with both eyes. These 2 patients were also tested on the Lanthony desaturated D-15 test and neither made any major errors (i.e., errors crossing the hue circle). Neither patient reported noticing any problems with his colour vision; indeed, Case 8 was an electrician before his illness and Case 6 claimed to have passed the Ishihara test while serving in the Armed Forces. Given that Case 6's deficit on the anomaloscope was monocular and that unilateral colour blindness is rare, we favour the hypothesis that his colour defect was acquired. We are unable to make a firm decision on Case 8; but given that he passed the Ishihara test for congenital colour blindness we tentatively suggest his defect is also acquired. Although there are reports (e.g., Tokuda and Yasuma, 1983) of subjects who make errors on pseudoisochromatic plates yet have a normal Rayleigh match (Pigmentfarben-anomalie), it surprised us to find the converse: a subject who could pass the Ishihara test while being diagnosed as virtually dichromatic on the anomaloscope.

Although the midpoints for most of the subjects are within normal limits (defined as within 2.58 SD of the mean) on this test, in 34/36 eyes the mid-matching point is shifted towards green compared to the control group. This means that in general the MS patients required more green in the red/green mixture than the control group. A Mann-Whitney test comparing the patient's 'good' eye (defined arbitrarily as that eye having the mid-matching point closest to the mean of the control group) with the control group shows that the two groups are very significantly different from each other ($P < 0.0001$, two-tailed). Therefore, compared with control subjects, the settings of the MS patients on the Rayleigh equation are significantly deuteranomalous (*see* Discussion).

A second point of interest is the width of the matching range of the patients. As fig. 6 shows, 1 patient (Case 8) would accept the full range of 82 scale units with his worse eye. Pickford and Lakowski (1960) recommend that subjects whose matching range is about two or more times the normal *modal* range be defined as 'colour weak'. The modal range for the control subjects was four scale units. If we take twice the modal range as our definition of colour weak this defines 6 subjects (9 eyes) as abnormal (*see* Table 2). This includes the 3 subjects who had the anomalous midpoints. The numbers in the Table represent the ratio of the patient's range to the modal control group range; so a value of 2.0 or above is 'colour weak' using our criterion.

Do patients with MS in general accept a larger matching range than control subjects? This hypothesis was tested with a Mann-Whitney test. However, there was no significant difference between the matching ranges of the control group and either the patients' 'good' or 'bad' eyes, the 'good' eye being defined as that eye with the smaller range of settings ($P > 0.05$, two-tailed, in both cases). This is an important result because it means that the deuteranomalous shift in the midpoint in MS is not simply associated with a larger matching range. Colour discrimination can still be acute (*see*, e.g., the very small matching range of Case 1). In this regard, many of the patients in fig. 6 resemble mild deuteranomalous trichromats (but *see* Discussion).

Results for the Engelking-Trendelenburg (blue/green) equation are shown in fig. 8. As in fig. 6, the range of mixture settings that the patient would accept as a match to the standard are compared with a control group mean (± 2.58 SD). In this figure, the mid-matching points for the patient group all fall within the normal limits. Patient S9, who accepted a relatively small range on the Rayleigh equation, here accepted the full range of blue/green mixtures with both eyes. This subject passed the Farnsworth F2 plate for congenital tritanopia. Two of the cases (6 and 8) who fell outside of the normal limits on the Rayleigh equation did not take part in this experiment.

TABLE 2. MATCHING RANGES OF THE PATIENTS ON THE TWO EQUATIONS DIVIDED BY THE MODAL MATCHING RANGE OF THE CONTROL GROUP ON THE SAME EQUATION*

Case		*Red-green range/ modal red-green range*	*Blue-green range/ modal blue-green range*
1	RE	0.38	0.19
	LE	0.25	0.5
2	RE	1.5	7.5
	LE	0.75	7.0
3	RE	3.75	10.25
	LE	3.75	9.13
4	RE	0.75	7.5
	LE	0.75	3.0
5	RE	0.75	0.19
	LE	1.5	2.5
6	RE	1.5	
	LE	4.75	
7	RE	0.75	1.88
	LE	0.5	0.63
8	RE	20.5	
	LE	17.75	
9	RE	1.25	10.25
	LE	1.5	10.25
10	RE	1.25	1.88
	LE	4.0	2.25
11	RE	0.5	2.5
	LE	0.5	2.0
12	RE	1.0	1.38
	LE	1.5	2.0
13	RE	1.75	4.0
	LE	1.75	7.13
14	RE	2.75	1.25
	LE	3.25	1.13
15	RE	0.75	2.88
	LE	1.5	4.5
16	RE	2.0	1.38
	LE	1.75	1.13
18	RE	0.75	2.63
	LE	1.25	2.63

* A value of unity would show that the patient had the same matching range as the control group mode; a value of 2.0 or above may be considered colour weak. RE = right eye; LE = left eye.

Unlike the results for the red/green equation, the mid-matching points for the patient group do not appear to lie systematically on one side of the mean for the control group. Indeed Mann-Whitney tests comparing the mid-matching points of the control group with the patients' 'good' and 'bad' eyes (defined as above) were not significant ($P > 0.05$, two-tailed). Moreover, a Mann-Whitney test showed there is no significant difference between the matching ranges of the patients 'good' and 'bad' eyes and the matching ranges of the subjects in the

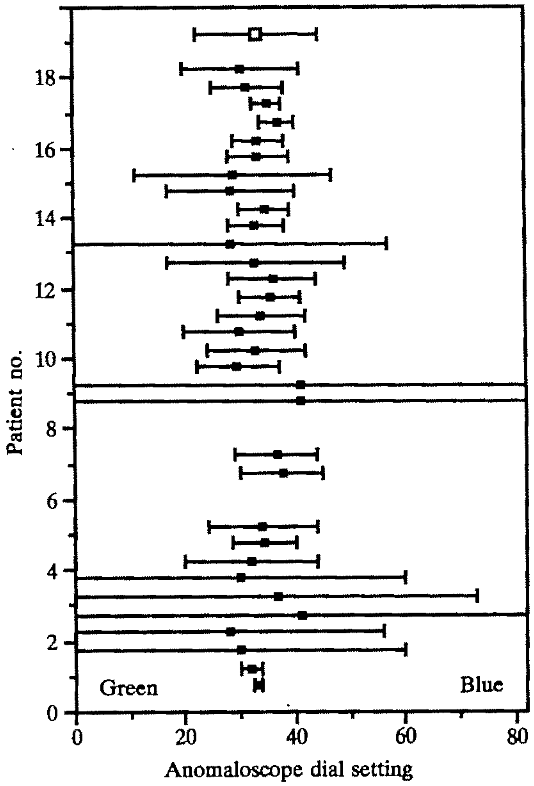

FIG. 7. Matching ranges and mid-matching points on the Engelking-Trendelenburg equation of 16 subjects with MS. The abscissa plots the scale setting of the anomaloscope: a value of 0 represents the most saturated green and 82 the most saturated blue that the instrument could produce. Other details as fig. 7.

control group ('good' eye defined as that eye with the smaller matching range, $P > 0.05$, two-tailed in both cases). However, the modal range for the control group was 8 scale units; more than half of the patients (11/18, 61%) have matching ranges for at least one eye greater than 2.0 times this value (*see* Table 2). Given that congenital tritanopia is so rare we favour the hypothesis that the colour defect in these patients is acquired.

Of the 4 patients who both performed abnormally on the Rayleigh equation and also performed the Engelking-Trendelenburg equation, 2 were shown to be defective on both tests.

Comparison of contrast sensitivity and colour vision measurements

As outlined in the Introduction, it has been proposed that the L-M cells in the lateral geniculate nucleus could perform two tasks, multiplexing information on both the chromatic and spatial attributes of a stimulus. If a demyelinating lesion should disrupt communication between the retina and the lateral geniculate we can predict that performance on the Rayleigh equation should broadly correlate with performance on the spatiotemporal task. However, as the parvocellular units that receive opposed inputs from short-wave cones and some combination of long and middle-wave cones (S-(L and M) cells) are relatively unimportant for spatial vision, we can predict that performance on the Engelking-Trendelenburg equation should not correlate with performance on the spatiotemporal task.

We decided to specify the contrast sensitivity deficit at any particular point in spatiotemporal space by differencing the threshold contrast sensitivities (in dB) of the left and right eyes. Similarly, the colour vision deficit was specified by differencing the range settings (in scale units) of the left and right eyes. It should be stressed that this procedure was not to classify either a colour or spatial frequency deficit but to provide an index of the relative degree of damage between the two eyes.

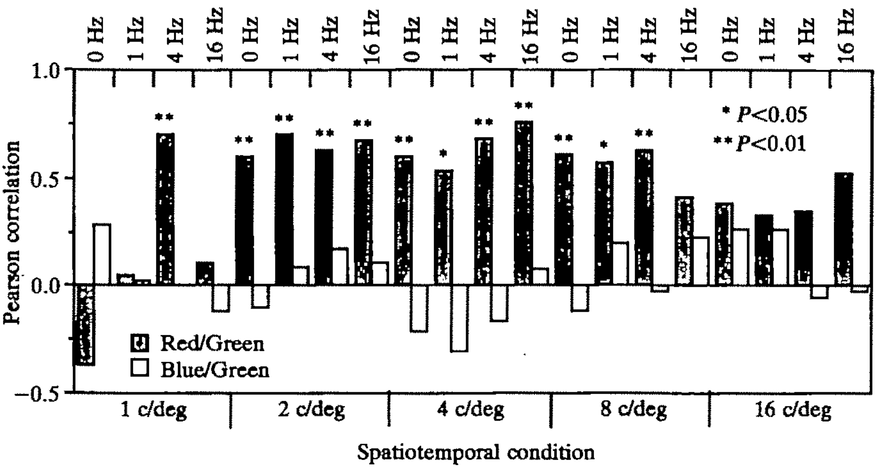

FIG. 8. Histogram of the Pearson correlations between colour deficit and contrast sensitivity deficit. The colour deficit was defined as the difference between the eyes in the range settings measured in scale units. The contrast sensitivity deficit for a particular spatiotemporal point was defined as the difference between the eyes in contrast threshold measured in dB. A single asterisk denotes a correlation significant at the 95% confidence level and a double asterisk significance at the 99% level (both two-tailed). At the higher spatial frequencies, the contrast thresholds of some subjects corresponded to contrasts of 77% and above (a nonlinear range on our screen) and so were discarded from this analysis; hence the sample size differs in different conditions. For the red/green equation, n = 18 except for the following spatiotemporal conditions: 1 c/deg, 16 Hz (n = 17), 2 c/deg, 4 Hz (n = 17; 8 c/deg, 16 Hz (n = 17); 16 c/deg, 0 Hz (n = 16); 16 c/deg, 1 Hz (n = 14); 16 c/deg, 4 Hz (n = 15); 16 c/deg, 16 Hz (n = 8). For the blue/green equation, on which 2 of the subjects were not tested, n is 2 less than the sample size for the red/green equation for each corresponding spatiotemporal condition.

With only one exception, all of the correlations with the differences between the range settings on the Rayleigh equation and the differences between the threshold contrast sensitivities at a particular spatial and temporal frequency are higher than the analogous correlations for the Engelking-Trendelenburg equation. The histogram in fig. 8 shows the results. Along the abscissa is plotted the particular spatiotemporal condition; the ordinate plots the Pearson correlation coefficient. None of the correlations between the range difference on the Engelking-Trendelenburg equation and the threshold difference at a particular spatiotemporal point is statistically significant ($P > 0.05$); more than half (12/20) of the analogous correlations for the Rayleigh equation are (the figure gives the confidence intervals).

With only one exception, however, the correlations with the red/green colour deficit are not significantly different from chance at the very lowest and highest spatial frequencies. These conditions that do not provide a strong correlation are not unexpected. The inability of a number of subjects to detect any gratings of the highest spatial frequency may account for the lack of significant correlations with the red/green colour deficit at 16 c/deg. At the lowest spatial frequency where three of the four correlations are not significantly different from chance, the magnocellular cells may provide a suitable achromatic pathway for detection of these gratings and hence a strong correlation with the red/green colour deficit would not be expected. The implication of these correlations is that in MS, colour discrimination losses that depend on L-M cells are associated with contrast sensitivity losses, whereas colour discrimination losses that depend on S-(L and M) cells are not.

DISCUSSION

The main findings of this study are (1) that MS causes varied spatiotemporal contrast sensitivity losses; (2) that MS causes acquired red/green and blue/green colour vision deficits; and (3) that the red/green colour deficit correlates strongly and positively with contrast sensitivity loss whereas the blue/green colour deficit does not.

With regard to the contrast sensitivity measures, we should point out that by making inter-eye comparisons rather than comparisons with a control group we do not make the assumption that our subjects have one entirely normal eye. Such an assumption would indeed be a difficult one to support. This is because both optic nerves are often damaged in MS. For example, Ulrich and Groebke-Lorenz (1983) examined histologically both optic nerves in 18 cases of MS; only one of the 36 optic nerves showed no evidence of demyelination, and yet in only 8 of the 18 patients had a diagnosis of unilateral or bilateral optic neuritis been reported. Our assumption in the present study is merely that the contrast sensitivity loss is greater in one eye than in the other.

With this caveat in mind, our results conflict with those of Brussell *et al.* (1984) who found that temporal modulation had no effect on the stationary contrast sensitivity functions for their patients. We believe this is because the patients in their study were instructed to make eye movements (Brussell *et al.*, 1984, p. 302); this of course makes it impossible to specify the temporal frequency of the gratings and could even nullify the effects of temporal modulation. This is supported by their own fig. 1 which shows little or no difference between the contrast sensitivity functions for stationary and moving gratings. It is well established that the bandpass characteristic of the contrast sensitivity function measured with stationary gratings becomes low-pass with temporally modulated gratings (Robson, 1966). In some of our patients we observed the pattern of results described by Hess and Plant (1985), that is, a decrease in the deficit with increasing temporal frequency, but for gratings of low spatial frequency only. It is intriguing to note that this pattern of loss would fit a selective loss in the parvocellular pathways.

One reason why we may not have found more exemplars of Hess and Plant's condition is because their measurements extended to spatial frequencies as low as 0.2 c/deg, whereas ours began at 1 c/deg. The nature of the contrast sensitivity losses that we observed are closest in agreement to those of Medjbeur and Tulunay-Keesey (1985), who demonstrated a number of temporal and spatial contrast sensitivity losses in patients with optic neuritis and MS. We believe that an explanation for these results may lie partly in the fact that demyelinating lesions of variable severity appear to be placed randomly within the anterior visual pathway (Ulrich and Groebke-Lorenz, 1983).

Part of our second result, that MS may cause a red/green colour deficit (6/18 patients), is consistent with the work of Cox (1961), whose study has been marshalled to support the hypothesis that optic nerve damage leads to an acquired type II colour vision deficit. Support for the notion that MS may be associated with some 'pseudo-deuteranomaly' comes from Grützner (1966) and Marré and Marré (1986). Verriest (1963) also reports anomaloscope matches to be deuteranomalous in optic neuritis, although the effect is described as 'a general enlargement of the matching range without a clear shift to the green' (cited in Foster, 1986, p. 163). Nagel (1905, cited in Pokorny and Smith, 1986) also described a red/green colour defect in optic neuritis. The subtle shift of the Rayleigh match to the green that we found in our patients taken as a group was not associated with an enlarged matching range and we emphasize that the mid-matching points of the great majority of our patients fall within normal limits on this test. Indeed, the existence of the shift might be treated with some caution since between testing the patient and control groups we were obliged to replace the anomaloscope bulb; however, the evidence that we have been able to gather does not reveal any systematic change in the calibration of our instrument. Furthermore the experimental and control groups were run at different times of the year and seasonal variations in anomaloscope measures have been reported (e.g., Richter 1948; Boles-Carenini, 1954).

Two of the patients tested were shown to be abnormal on both the Rayleigh and Engelking-Trendelenburg equation, consistent with a severe type II acquired defect. A majority (11/18 patients) had matching ranges on the Engelking-Trendelenburg equation that betray a type III (tritan-like) deficit, although the mid-matching points for all our patients on this equation are within normal limits. This type of deficit has been reported in many diseases of the eye, as well as systemic diseases (Pokorny *et al.*, 1979). However, it is not generally considered to be symptomatic of MS or optic nerve damage unless it occurs in conjunction with a red/green loss (and would hence be categorized as a severe type II loss). This defect has also been reported in some patients (2/5) with retrobulbar neuritis by Ohta (1970) using the Farnsworth Panel D-15. Other reports of tritan-like deficits have been reported by experimenters using the Lanthony D-15 test (most recently, Fredriksen *et al.*, 1986). The type III defect may be caused by a lesion to any point along the visual pathway (Pokorny *et al.*, 1979, p. 80).

It should be made explicit that, as with the contrast sensitivity measures, we cannot classify the colour vision deficit in MS in any general terms. Some individual patients show a type II acquired defect and others a type III. We suspect that this is because the demyelinating lesions in MS are not restricted simply to the optic nerve, damage to which is generally thought to be the cause of type II acquired defects, but may occur at any point along the visual pathway. Furthermore, Kirshner *et al.* (1985) provided MRI evidence for scattered cerebral lesions in 35/35 patients with MS (definite, probable and possible cases). Ormerod *et al.* (1986) have recently demonstrated such lesions in patients presenting with optic neuritis. In our patients, with long-standing MS, a plaque of demyelination in the visual cortex might produce a number of perceptual difficulties that, in the interests of parsimony, most workers might ascribe to optic nerve damage. What is clearly required at some future date are MRI, contrast sensitivity and anomaloscope data on the same patients with MS in order to produce a correlative study between the type of visual defect and the site of the demyelinating lesions. We would predict that those patients with type II acquired colour vision deficits would have lesions confined predominantly to the optic nerve; those with type III acquired defects would have lesions at different or additional sites along the visual pathway.

Although the 'double-duty' cells reported by Derrington *et al.* (1984) were found in the lateral geniculate nucleus of their animals, the striking correlations that we have found between red/green colour vision and contrast sensitivity performance need not necessarily implicate plaques of demyelination in this region in our patients. A more parsimonious conclusion would be that the optic nerve fibres providing input to the appropriate cells have been damaged by the disease. Once again we do not propose that this demyelination is selective; indeed, the very fact that blue/green colour vision is also disrupted in our patients argues against such a conclusion. Instead, our conclusion is that the varied spatiotemporal contrast sensitivity and colour vision deficits in MS that have been reported in the literature are likely to reflect damage to the same cells in the visual pathway. If these cells perform 'double-duty', then our results are consistent with a model of random demyelination at many points along the visual pathways, including the optic nerves, tracts and radiations, rather than selective or more disruptive damage to fibres carrying information about colour (Fallowfield and Krauskopf, 1984) or luminance (Zisman *et al.*, 1978).

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THE ABILITY OF PATIENTS WITH BRAIN DAMAGE TO GENERATE MENTAL VISUAL IMAGES

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SUMMARY

The ability to form mental visual images was investigated in normal controls, patients with localized brain damage, and patients with Parkinson's disease. Verbal and visuospatial imagery tasks were compared with tasks in the same modality that did not demand the formation of visual images. In the verbal part, memorizing of word pairs was tested for abstract words, concrete words without imagery instruction, and concrete words with imagery instruction. In the visuospatial part, three tests required the evaluation of spatial features of imagined letters. In one of them mental rotations had to be performed in the exploration of the imagined stimulus. The visuospatial control tasks tested the ability to judge the position of perceived dots and mentally to rotate a seen mannekin.

The pattern of results was determined mainly by the differential sensitivity of visuospatial and verbal tasks to right and left brain damage, respectively. Multidimensional scaling of correlations between test results did not show a close relationship between the results of verbal and visuospatial imagery tasks, but suggested that brain damage affected visuospatial imagery tasks differentially from visuospatial control tasks. Analysis of single cases showed that patients with lesions of the left temporo-occipital region failed to benefit from the imagery instruction in the memorizing of concrete words. These patients could nonetheless solve correctly the visuospatial imagery tasks. Possibly this dissociation is due to differences in the amount or the quality of information conveyed by the visual images rather than to the verbal or visuospatial mode of processing to which the images are subjected.

INTRODUCTION

More than a hundred years ago, Charcot (1883) gave the first neurological case report of a man who lost the ability to conjure up mental visual images as a sequel of a stroke. Since then numerous case reports have confirmed that visual imagery can be affected by localized brain damage (*see* Farah, 1984, for a review). In all these cases the loss of imagery was accompanied by a similar impairment of visual perception, the only exception being made by 2 cases reported by Brain (1954). Case 1, however, was able to describe the appearance of objects which he claimed to be unable to imagine, and the psychologists who examined him, Drs McFie

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and Zangwill, raised the question as to whether the patient's loss of visualization could be 'neurotic' (p. 289). Case 2 did experience mental visual images but was unable to evoke them voluntarily. He could describe the appearance of imagined objects with eyes opened but not with eyes closed.

Case reports of loss of visual imagery thus support the notion that there are common stages in the processing of mental visual images and visual perceptions, but they do not permit conclusions concerning the processes that generate visual images. Cognitive theories of visual imagery, on the other hand, have made assumptions about the relations between memory, imagery, and perception which lead to the expectation that the generation of mental visual images is a distinct capability that can be selectively impaired by brain damage.

For example, Paivio's dual coding model of mental representations (Paivio, 1979, 1986) assumes that in the brain there are two types of symbolic systems specialized for the storage and processing of verbal and nonverbal information, respectively. Mental visual images are generated only by nonverbal systems. Nonverbal systems are also responsible for visuospatial processing. Damage to nonverbal systems can hence impair both the generation of mental visual images and the visuospatial processing of either mental images or perceptions, but these two types of impairment need not necessarily be tightly correlated. Moreover, a damage to the nonverbal system which is responsible for the generation of visual images should become manifest also when mental images are to be exploited for a verbal rather than a visuospatial task. For instance, it should lead to an inability to benefit from the use of visual imagery for the enhancement of verbal episodic memory.

Another approach to the exploration of visual imagery has been initiated by Kosslyn (1983, 1987). Its basic assumption is that visual images are derived from information in long-term memory which is transferred to a visual buffer. The visual buffer is a structure that is also employed in visual perception, and further processing of visual images and visual percepts then follows a single common path. Impairment in the generation of mental visual images without a concomitant visuoperceptual impairment should occur if the translation of information from memory into the visual buffer is affected by localized brain damage (Farah 1984).

The purpose of the following study was to look systematically for deficits in the generation of mental visual images caused by brain damage. Verbal and visuospatial imagery tasks were compared with tasks in the same modality which did not call for the formation of mental visual images in order to establish whether any of the investigated brain lesions would give rise to a selective impairment of the capacity to generate mental visual images.

METHODS

All patients were examined with five visuospatial and three verbal tasks.

Visuospatial imagery tasks

Corners. This and the following right-left test were based on an imagery task which Brooks had shown to be sensitive to visuospatial interference (Brooks, 1968). The patient was asked to imagine a capital letter composed of single lines and to count the corners, a corner being defined as a point where lines either meet or end. The letter was to be of Helvetica type, that is, an 'I' has 2 corners and a 'K' has 5. Twelve letters were tested, and 1 point was given for each correct answer.

Right-left. Again, the patient was asked to imagine an upper case letter in Helvetica type composed of single lines, but this time she or he was asked to imagine a mental walk around the letter, starting from a point on its left hand side and circling clockwise. On every corner the patient was required to say whether she or he had to turn right or left as judged by the direction of the imagined movement. For an 'L' the correct sequence is right-left-right-right, for a 'T' left-right-right-left-right. Again, 12 letters were tested, and 1 point was credited for every correct sequence of responses.

Words. This test was similar to a task which Podgorny and Shepard (1978) had introduced into imagery research to prove the functional equivalence between imagery and perception. The patient was shown a sheet with 3 adjacent rectangles of 5 cm height and 3 cm width drawn on it. Each rectangle contained 2 digits of 2 mm height. The patient was asked to imagine a three-letter word written in capital letters in Helvetica type, each letter being composed of 5 mm thick bars and filling the space of one rectangle. Samples of these letters were shown during the demonstration of the task. The task was to judge which of the digits would fall upon a bar and which would not. During performance of the task the single letters were repeated to the patient to prevent errors arising from forgetting the word or from difficulties in spelling it. Ten words were tested and 1 point was given for each correct response, yielding a maximum of 6 points per item.

Visuospatial control tasks

Mental rotation. It has been shown that the time course of the mental rotation of imagined shapes is the same as that of perceived stimuli, i.e., both show a linear relationship between the angle of the rotation and the time necessary to perform it (Cooper, 1975). Hence mental rotation appears to be a stage in visuospatial processing where imagery and perception converge and can serve as a control task for deficits that affect the manipulation but not the generation of mental visual images. The test used was an adaptation of Ratcliff's mannekin test (Ratcliff, 1979). The patient was shown 32 cards of 7 cm width and 10 cm height. On each card was drawn a mannekin that held a ball in one hand which was the right in 16 and the left in the other 16 cards. The mannekin was either upright or reversed and either seen from behind, from the front, from the left side, or from the right side. Each of the 2 × 2 × 4 combinations of hand, position and view appeared once in random order and the patient was asked to say whether the ball was in the right or the left hand. Each correct answer was credited 1 point. If it is assumed that right-left judgements are made with reference to the individual's own body, then the only condition in which no mental rotation was needed was the one where the mannekin was upright and seen from behind. Two patients with left brain damage and 1 with bilateral lesions committed errors in this condition and were excluded from this test.

Position. This test was aimed at assessing the capacity to estimate angles and spatial positions of preceived stimuli. The patient was shown a sheet of 14 cm height and 21 cm width with two similar drawings filling its upper left and lower right quadrants. Each drawing showed a red dot and 2 digits of 2 mm size. The task was to compare both drawings and to judge for each of the digits whether its position relative to the dot was the same or not. The patient was advised to consider the distance as well as the angle. Eighteen items were given, and in 6 of them both digits had the same position, in 6 both had different positions, and in 6 one position was different and the other the same. One point was given for each correct comparison, hence 2 points could be obtained for each item.

With the exception of the mental rotation task, each task was first demonstrated by drawings, and comprehension of the instruction was tested by practice items.

Verbal memory tasks

Paired associate learning was tested: after 8 pairs of nouns had been read aloud by the examiner with intervals of approximately 5 s between them, the patient was to respond with the second word of each pair when probed with the first. The ordering of the response cues was different from that of the presentations of the pairs. Three lists were tested.

Abstract. The pairs were composed of nouns with rating below 3 on a seven-point scale of imageability of German words (Mitterndorfer, 1978): 'courage and cheerfulness, performance and success, antiquity and politics, knowledge and stupidity, question and chance, north and west, thing and culture'.

Two lists were composed of nouns rated above 6 on the seven-point scale: 'fur and bathtub, donkey and cart, mouth and watch, lion and barber, violin and drum, parrot and policeman, paper-basket and mouse, apple and coffee'; and: 'chicken and hat, saucepan and potato, motorcycle and toboggan, ski-pole and lemon, shoe and cigar, tombstone and crocodile, flower and ring, monkey and cow'.

The two concrete lists were randomly assigned to one of the following conditions.

Concrete. The pairs were given without any further instruction concerning the strategy to be applied for memorization. After the test the patient was asked how she or he had proceeded. One control patient reported having used an imagery strategy. Consequently, the result was regarded as belonging to the imagery condition. The other patients had either tried to find semantic or phonemic similarities between the words, had rehearsed the pairs, or reported no particular strategy at all.

Imagery. The patient was instructed to form a composite image depicting both objects named and to concentrate on the mental image in order to memorize the pair. She or he was told that she or he was free to choose either a realistic or a bizarre image, and examples for both kinds of images were given for a pair from the previously learned concrete words list. The patient was asked not to report the content of her of his image verbally but to say 'yes' or nod as soon as she or he had succeeded in forming one. Presentation proceeded only after the patient had acknowledged the formation of an image.

The test battery was given in a fixed order: abstract—corners—right-left—concrete—words—imagery—position—mental rotation. Clinical neuropsychological assessment of patients with localized brain damage was performed in a separate session beforehand.

PATIENTS

Consecutive patients were admitted for testing. Three groups of patients were examined: patients with circumscribed brain lesions, patients with Parkinson's disease, and controls who were in neurological care because of diseases of the spine, the peripheral nerves or muscles. A recent CT scan was available in all patients with circumscribed brain lesions and was re-evaluated by the author for classification of lesions. Lesions were classified as 'anterior' or 'posterior' when they encroached on the cortex and were situated entirely in front of or behind a line drawn through the central region. Lesions which transgressed this line or were localized entirely within the white matter or basal ganglia were classified as 'other'. In patients with Parkinson's disease the degree of tremor, rigidity, akinesia and functional disability was assessed by means of the Columbia University rating scale (Duvoisin, 1970). All parkinsonian patients were between stages 2 and 4 of the Hoehn and Yahr scale (Hoehn and Yahr, 1967) and had adequate pharmacological treatment at the time of examination. All of them received L-DOPA and benserazid, several of them had additional treatment either with anticholinergic drugs or dopamine agonists. No patient was examined during an 'off' phase.

The verbal tasks were given to aphasic patients only if they made no semantic paraphasias in repetition and if phonemic paraphasias were not severe enough to compromise the comprehensibility of spoken words, and with the visuospatial tasks aphasic patients were tested only if they were able to write down the letters and words on dictation. If a patient failed to understand the instruction of one task she or he was nonetheless examined with the remainder; if she or he did not comprehend more than one instruction she or he was excluded.

A total of 195 patients were examined. The examination could not be performed in a further 13 patients who either failed to understand the instructions or were unable correctly to write down the letters and words of the visuospatial imagery tasks on dictation: 9 were aphasic (5 global, 2 Wernicke, 1 amnesic, 1 transcortical sensory), 2 had right brain lesions, 1 bilateral lesions and 1 Parkinson's disease. The number of patients who were either excluded from single tests or did not complete them because of extraneous reasons was 6 for words and position, 5 for mental rotation, 3 for right-left and the verbal tasks (plus the 1 control patient already mentioned for concrete words without instruction), and 2 for corners.

Table 1 shows the number, age, sex, aetiology, intrahemispheric localization and, in cases with left brain damage, the type of aphasia for each group of patients, as well as the scores of the patients with localized brain damage on Raven's coloured progressive matrices (Raven, 1965).

TABLE 1. DESCRIPTION OF PATIENTS

	Left brain damage	*Right brain damage*	*Bilat. brain damage*	*Parkinson's disease*	*Controls*
Sex	14F, 21M	12F, 27M	8F, 14M	16F, 24M	24F, 35M
Age (yrs)*	45.7±15.1 (24–76)	54.8±15.7 (24–81)	50.5±18.9 (18–73)	62.3±8.4 (44–78)	50.8±16.7 (20–83)
Aetiology					
CVD	21	23	10		
Tumour	10	14	5		
Trauma	4	2	7		
Localization:					
Anterior	7	13	2		
Posterior	14	14	3		
Other	14	12	17		
Aphasia	1 global 6 Broca 6 Wernicke 2 amnesic 2 not classified				
Coloured progressive matrices*	27.3±6.0	24.7±5.2	23.5±6.6		

* Mean±SD

RESULTS

Influence of age, sex, and severity of Parkinson's disease

Scores on all tests and negative correlations with age which were strongest for right-left (Pearson's $r = -0.45$, $P<0.0005$) and words ($r = -0.36$, $P<0.0005$) and weakest for mental rotation ($r = -0.12$, $P = 0.051$) and concrete words with an imagery instruction ($r = -0.12$, $P = 0.054$). MANOVAs did not show significant interactions between age and group for any of the tasks. Hence age affected performance equally across groups and its effect on the differences between groups could be partialled out by analyses of covariance.

Only on right-left did females score significantly worse than males (males: $6.5+4.1$, females: $4.5+3.9$, t test: $P<0.002$). There was, however, no significant variation of the distribution of sexes across groups ($\chi^2 = 7.7$, $P>0.10$).

In parkinsonians no significant correlations were found between test scores and any of the subscales or the total score of the Columbia University rating scale. There were no significant correlations between the doses of L-DOPA administered and any test results, nor did patients who received anticholinergic drugs differ significantly from those which did not.

Further analysis of data proceeded in three steps. First, correlations between test results were analysed. If generation of mental visual images is indeed a distinct capability, then the results of the tasks which call for it should correlate more strongly with each other than with the control tasks. Secondly, the question whether the patient groups differ in their capacity to form mental visual images was tackled by MANOVAs which were carried out for verbal and visuospatial tasks separately. A selective deficit of a patient group concerning only the imagery tasks should show up in an appropriate task by group interaction. Thirdly, the influence of the intrahemispheric location of lesions was analysed in patients with localized brain damage. Anterior, posterior, and other lesions were compared by means of MANOVAs. Because previous studies suggested the occipital and inferior temporal regions as the most likely site for being the cerebral substrate of visual imagery, patients with lesions of these areas were analysed individually.

Correlations between tests

Correlations between test results were computed for the whole sample and for each group of patients. To facilitate interpretation of the multiple relationships, the correlation matrices were subjected to multidimensional scaling. This procedure yields a spatial representation of the structure of relationships in which the order among the correlations is represented by the order among the Euclidean distances between points. A nonparametric multidimensional scaling procedure, smallest space analysis (SSA) based on monotonicity coefficients, was used (Guttman, 1967; Lingoes, 1979). To check the reliability of the results, multidimensional scaling was repeated with Spearman rank correlations and the ALSCAL program (Young *et al.*, 1978). The main structural relationships that will be interpreted were essentially the same with both methods.

Table 2 shows the monotonicity coefficients and fig. 1 the two-dimensional SSA representations of the correlations between tests for each patient group and for all patients taken together. The Guttman-Lingoes coefficients of alienation which express the goodness of fit between the original data and their SSA representations were between 0.04 and 0.14. Values below 0.15 are generally recognized as indicating a good fit (Brown, 1985).

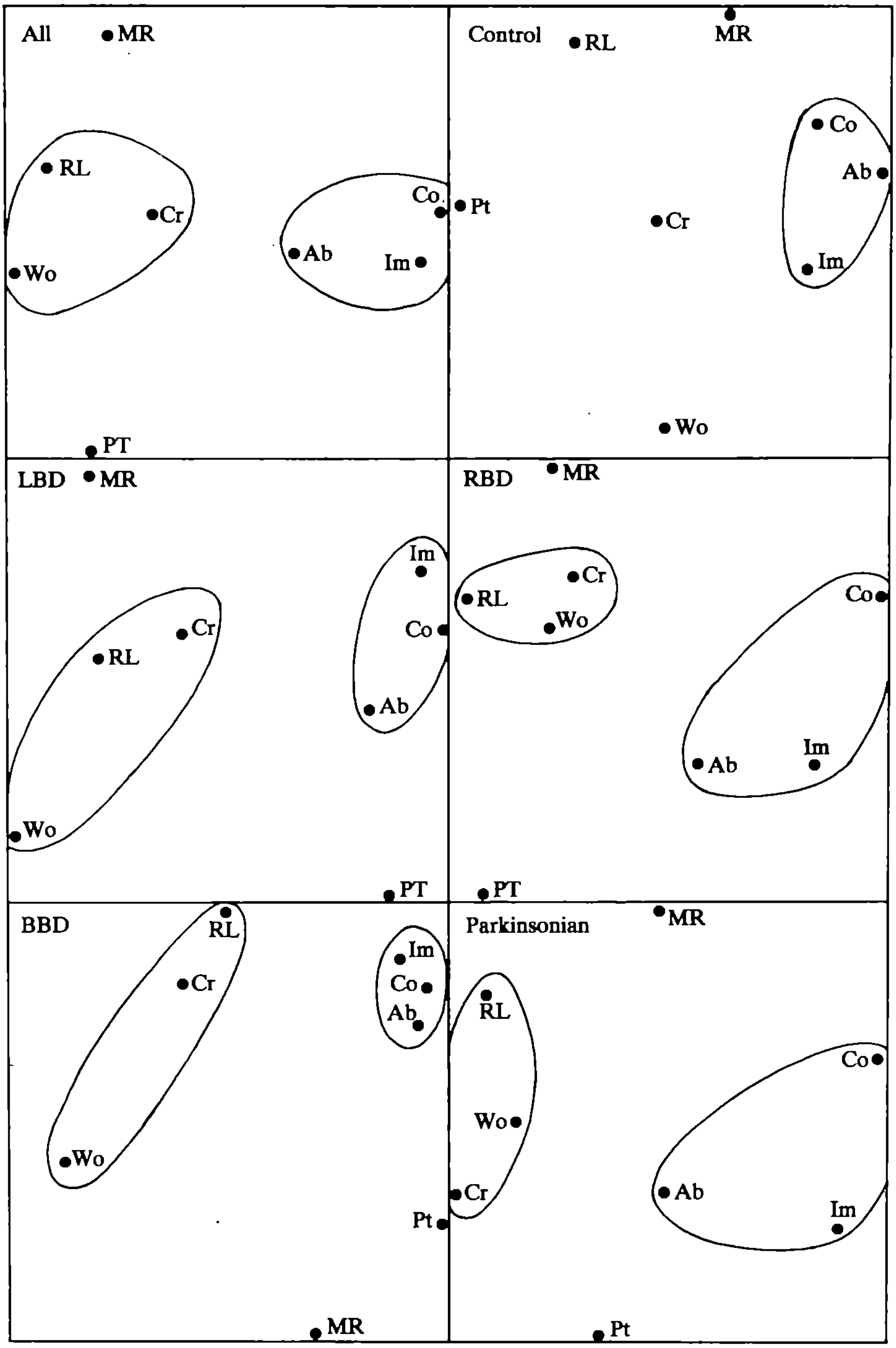

FIG. 1. Multidimensional scaling of correlations between test results. Ab = abstract; Co = concrete; Im = imagery; Cr = corners; RL = Right-left; Wo = words; Pt = position; MR = mental rotation. All = correlations for the whole patient sample; Control = only control group; LBD = only patients with left brain damage; RBD = only patients with right brain damage; BBD = only patients with bilateral brain damage; Parkinsonian = only parkinsonian patients. Within each representation the clusters unifying verbal tasks and visuospatial imagery tasks, respectively, are marked. The monotocity coefficients which were subjected to multidimensional scaling are shown in Table 2.

TABLE 2. CORRELATIONS BETWEEN TEST RESULTS

All patients

Co	0.64						
Im	0.66	0.66					
RL	0.50	0.38	0.38				
Wo	0.48	0.31	0.41	0.56			
Cr	0.55	0.45	0.51	0.65	0.66		
Pt	0.49	0.29	0.33	0.49	0.49	0.51	
MR	0.47	0.43	0.37	0.54	0.46	0.58	0.43
	Ab	Co	Im	RL	Wo	Cr	Pt

Controls

Co	0.65						
Im	0.64	0.73					
RL	0.48	0.53	0.43				
Wo	0.46	0.44	0.61	0.44			
Cr	0.62	0.60	0.62	0.61	0.68		
Pt	0.40	0.40	0.44	0.50	0.44	0.60	
MR	0.53	0.56	0.51	0.52	0.39	0.66	0.50
	Ab	Co	Im	RL	Wo	Cr	Pt

Left brain damage

Co	0.69						
Im	0.60	0.68					
RL	0.51	0.43	0.48				
Wo	0.50	0.28	0.34	0.61			
Cr	0.50	0.56	0.65	0.78	0.59		
Pt	0.59	0.56	0.38	0.41	0.41	0.44	
MR	0.48	0.48	0.37	0.63	0.45	0.55	0.36
	Ab	Co	Im	RL	Wo	Cr	Pt

Right brain damage

Co	0.54						
Im	0.62	0.49					
RL	0.51	0.27	0.32				
Wo	0.56	0.34	0.37	0.62			
Cr	0.51	0.40	0.50	0.63	0.67		
Pt	0.54	0.19	0.29	0.49	0.39	0.38	
MR	0.40	0.31	0.31	0.58	0.52	0.62	0.29
	Ab	Co	Im	RL	Wo	Cr	Pt

Bilat. brain damage

Co	0.71						
Im	0.71	0.81					
RL	0.38	0.40	0.60				
Wo	0.18	0.15	0.15	0.34			
Cr	0.38	0.41	0.54	0.65	0.54		
Pt	0.47	0.56	0.38	0.29	0.29	0.28	
MR	0.35	0.26	0.18	0.15	0.32	0.32	0.57
	Ab	Co	Im	RL	Wo	Cr	Pt

Parkinson's disease

Co	0.65						
Im	0.66	0.58					
RL	0.54	0.35	0.29				
Wo	0.58	0.28	0.46	0.58			
Cr	0.66	0.26	0.37	0.56	0.62		
Pt	0.71	0.22	0.48	0.44	0.50	0.52	
MR	0.47	0.50	0.41	0.56	0.49	0.46	0.39
	Ab	Co	Im	RL	Wo	Cr	Pt

Abbreviations as in fig. 1.

The smaller is the distance between the data points representing two tests, the stronger the positive correlation between them. Tests that share a component should be represented adjacent to each other (Brown, 1985).

In all groups verbal tasks showed a close mutual relationship that separated them from the visuospatial tasks. In all groups of brain-damaged patients a second cluster of correlations combined the visuospatial imagery tasks and separated them from the two other visuospatial tasks, whereas in the control group no salient association appeared to distinguish the visuospatial imagery tasks from the remainder of the visuospatial tasks. There was no community between visuospatial imagery tasks and the verbal imagery task either in the whole sample or in any subgroup of patients.

The observation that the association between visuospatial imagery tasks was relatively stronger in brain-damaged patients than it was in controls may indicate that brain damage affected a component which is common to these tasks. This component could be the formation of mental visual images. Possibly its influence did not show up in the results from the normals because they had no particular difficulties in forming adequate mental images and their success was determined mainly by their general skill in coping with task demands and by their capacity to manipulate and evaluate the correctly formed mental images. Since the association was present in all brain-damaged groups it cannot be attributed exclusively to the effect of a lesion within one hemisphere. If, for example, the generation of visual images depended on the integrity of a region in, say, the right hemisphere, then the association should show up only in those groups that contain right brain-damaged patients, i.e., right brain-damaged, bilateral brain-damaged and perhaps also parkinsonian patients, but not in patients whose lesions reside exclusively in the left hemisphere.

The SSA representations permit an alternative explanation for the relationship between visuospatial imagery tasks: in all representations that show the separation between visuospatial tasks with and without imagery, it would also be possible to delineate a continuous subspace which unites the visuospatial imagery tasks and all verbal memory tasks and separates both of them from the remainder of the visuospatial tasks. A possible interpretation of this distinction would be that the visuospatial imagery tasks as well as all verbal memory tasks demanded the retrieval of information from memory whereas there was no memory component in the other visuospatial tasks.

TABLE 3. RESULTS OF ALL TESTS FOR ALL GROUPS

	Controls		*Left brain damage*		*Right brain damage*		*Bilat. brain damage*		*Parkinson's disease*		*Maximum score*
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Visuospatial											
Corners	10.9	1.3	10.3	2.0	9.3	2.6	8.7	3.0	9.5	2.0	12
Right-left	7.3	3.8	6.4	3.9	4.6	3.9	3.1	3.1	4.2	3.9	12
Words	54.0	5.1	53.5	4.7	49.5	5.9	46.4	8.2	45.9	8.9	60
Mental rotation	30.0	2.3	28.3	3.8	27.7	4.0	27.2	3.7	29.2	2.7	32
Position	28.9	3.5	28.6	3.5	23.7	4.7	25.1	2.8	26.2	4.2	36
Verbal											
Abstract	2.6	1.8	1.6	1.5	2.2	1.4	1.6	1.0	1.7	1.8	8
Concrete	3.6	1.9	1.4	1.6	3.4	2.2	2.2	1.6	2.3	1.7	8
Imagery	6.5	1.8	3.2	2.8	6.5	1.5	3.9	2.7	4.1	2.5	8

Differences between groups

Table 3 shows the results of all tests for all groups. For statistical analysis the results were converted to z scores of the total sample, and MANOVAs were carried out for verbal and visuospatial tasks, respectively, with group as between subject factor, task as within subject factor, and age as covariate. First, a MANOVA was performed on the data of all groups, and then each pair of groups was compared by multiple MANOVAs, the probabilities of which were corrected

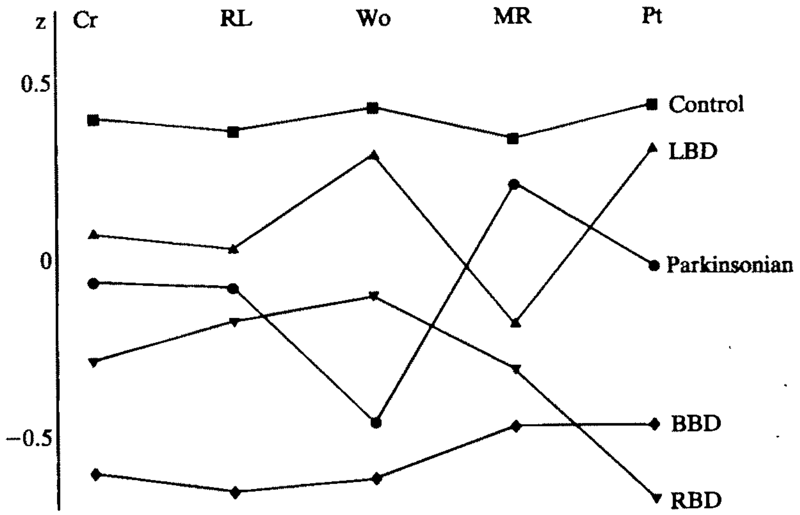

FIG. 2. Age-adjusted z-scores of visuospatial tests. Abbreviations as in fig. 7. The results of the MANOVAs performed on these data are given in Table 4.

TABLE 4. MANOVA OF VISUOSPATIAL TASKS

	Main effect (group)			*Interaction (task x group)*		
	F	*df*	*P*	*F*	*df*	*P*
All groups	10.93	4,178	<0.0005	2.91	16,538	<0.0005
Control vs LBD	6.04	1,87	0.016	1.05	4,85	>0.1
Control vs RBD	30.82	1,92	<0.0005*	2.14	4,90	0.082
Control vs BBD	41.44	1,72	<0.0005*	0.30	4,70	>0.1
Control vs Park.	12.05	1,95	0.001*	4.74	4,93	0.002*
LBD vs RBD	6.14	1,60	0.016	2.21	4,64	0.077
LBD vs BBD	11.1	1,46	0.002*	1.36	4,44	>0.1
LBD vs Park.	0.20	1,69	>0.1	6.64	4,67	<0.0005*
RBD vs BBD	0.48	1,51	>0.1	1.15	4,49	>0.1
RBD vs Park.	1.84	1,74	>0.1	6.27	4,72	<0.0005*
BBD vs Park.	3.87	1,54	>0.1	0.90	4,52	>0.1

LBD = left brain damage; RBD = right brain damage; BBD = bilateral brain damage; Park. = Parkinson's disease. * Significant at a global alpha level of 0.05 (Holms, 1979).

to a global alpha value of 0.05 (Holms, 1979). The age adjusted z-scores are shown in figs 2 and 3, and the results of the respective MANOVAs in Tables 4 and 5. The main effects of groups indicate differences in the general level of performance on visuospatial or verbal tasks, respectively. Main effects of task were eliminated by the conversion to z scores. A significant task × group interaction, however, indicates that there is a difference in the relative impairment of groups on different tasks within either the visuospatial or the verbal modality, or, put another way, that the profile of performance is different between groups.

Visuospatial tasks

The general level of performance on visuospatial tasks was reliably lower than in controls in patients with right brain damage, with bilateral brain damage, and with Parkinson's disease, and patients with bilateral brain damage were also significantly worse than those with left brain damage. There was a significant general task × group interaction. The post hoc comparisons showed that it was mainly due to the deviating profile of the parkinsonian patients' results. Within the parkinsonian patients, z scores of words were significantly lower than those of all other visuospatial tests (words vs corners: $t(39) = 2.82$, $P = 0.007$; words vs right-left: $t(39) = 2.29$, $P = 0.028$; words vs points: $t(39) = 2.84$, $P = 0.007$; words vs mental rotation: $t(39) = 4.33$, $P = 0.0005$), whereas no other group showed a selective impairment on the word task. A further interaction, however, appears to stem from a different impairment of left and right brain-damaged patients on the visuospatial control tasks. Left brain-damaged patients scored significantly better than right brain-damaged patients on position ($F(1,68) = 15.41$, $P<0.0005$) but not on mental rotation ($F(1,68) = 0.249$, $P = 0.67$). It thus seems that the two visuospatial control tasks tapped capacities that are differentially affected by right or left brain damage, but it should be emphasized that this dissociation is not directly relevant to the generation of mental visual images.

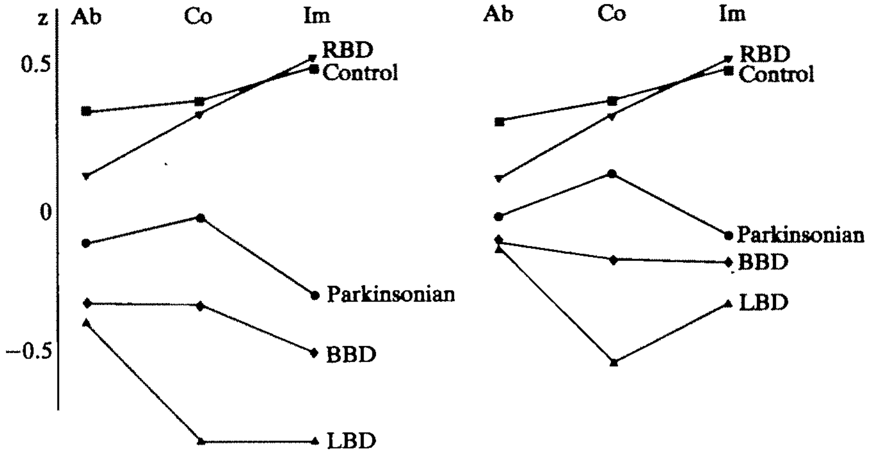

FIG. 3. Age-adjusted z scores of verbal tests. Left hand side: scores of all patients; right hand side: scores of patients who remembered more than a total of three pairs out of all three lists. Abbreviations as in fig. 1. The results of the MANOVAs performed on these data are shown in Table 5.

Verbal tasks

A first MANOVA including all patients revealed a general impairment of verbal memory in patients with left brain damage, bilateral brain damage, and with Parkinson's disease. There was also a significant group x task interaction. It

TABLE 5. MANOVA OF VERBAL TASKS

All patients

	Main effect (group)			*Interaction (task x group)*		
	F	*df*	*P*	*F*	*df*	*P*
All groups	17.04	1,187	<0.0005	2.18	8,370	0.028
Control vs LBD	42.7	1,87	<0.0005*	3.31	2,87	0.041
Control vs RBD	0.13	1,93	>0.1	0.57	2,93	>0.1
Control vs BBD	18.81	1,76	<0.0005*	1.24	2,76	>0.1
Control vs Park.	10.97	1,94	0.001*	1.41	2,94	>0.1
LBD vs RBD	35.34	1,70	<0.0005*	6.23	2,69	0.003*
LBD vs BBD	1.50	1,52	>0.1	1.21	2,52	>0.1
LBD vs Park.	4.84	1,70	0.031	1.58	2,70	>0.1
RBD vs BBD	17.37	1,58	<0.0005*	3.03	2,58	0.056
RBD vs Park.	9.66	1,76	0.003*	3.61	2,76	0.032
BBD vs Park.	1.10	1,59	>0.1	0.02	2,59	>0.1

After exclusion of patients with severe general verbal memory deficit

	Main effect (group)			*Interaction (task x group)*		
	F	*df*	*P*	*F*	*df*	*P*
All groups	6.55	4,159	<0.0005	0.91	8,318	>0.1
Control vs LBD	14.14	1,74	<0.0005*	1.24	2,74	>0.1
Control vs RBD	0.37	1,92	<0.1	0.48	2,92	>0.1
Control vs BBD	6.37	1,69	0.014	0.22	2,69	>0.1
Control vs Park.	5.02	1,86	0.028	0.49	2,86	>0.1
LBD vs RBD	10.44	1,57	0.002*	2.42	2,57	0.10
LBD vs BBD	0.60	1,34	>0.1	0.55	2,34	>0.1
LBD vs Park.	0.51	1,51	>0.1	1.03	2,51	>0.1
RBD vs BBD	5.29	1,52	0.026	1.0	2,52	>0.1
RBD vs Park.	3.29	1,69	0.074	1.65	2,69	>0.1
BBD vs Park.	0.29	1,46	>0.1	0.05	2,46	>0.1

Abbreviations as in Table 4. * Significant at a global alpha-level of 0.05 (Holms 1979).

appeared to be due mainly to the left brain-damaged patients' relatively good performance on abstract words: only within the left brain-damaged patients the z scores of abstract words were higher than those of concrete words without ($t(32) = 2.22$, $P = 0.034$) and with an imagery instruction ($t(32) = 2.29$, $P = 0.029$). This apparent preservation of memory for abstract words might stem from a floor effect: controls remembered only an average of 2.6 abstract word pairs, as compared with 3.6 concrete pairs without and 6.5 with an imagery instruction. Since the possible minimum score was zero, the possible range of impairment was smaller with abstract words than it was with concrete words. Inspection of the z scores suggests another difference of profiles which is more relevant to imagery. It appears that the three patient groups who had a general memory deficit also drew relatively less benefit from the imagery instruction than did the two groups who were not impaired. It is questionable, however, whether this difference of profile is indeed indicative of a specific inability to enhance verbal memory by imagery. It might stem from the results of patients whose general memory deficit was so severe that performance remained close to zero regardless of what kind of words were to be memorized and of what strategy they tried to use. To check for this possibility, a second analysis was carried out after exclusion of patients who did not remember more than a total of three pairs out of all three lists. The exclusion concerned 1 control patient, 12 patients with left brain damage, 6 with bilateral brain damage and 7 with Parkinson's disease. The z scores of the remaining patients are shown on the right side of fig. 3, the results of the MANOVA in the lower part of Table 5. The exclusion concerned virtually all patients who had scored zero with the abstract pairs and thus further reduced the range of possible differences for abstract words. Nonetheless, the group × task interaction lost statistical significance, and within the left brain-damaged patients no significant difference between z-scores could be found any longer. As it seems, the exclusion of patients who failed completely on all the verbal memory tasks had somewhat restored the sensitivity of the verbal memory of left brain damaged patients to the effect of word concreteness. Moreover, an inspection of fig. 3 shows that the gain of the left brain-damaged patients from the imagery instruction is now equivalent to that of the controls and of patients with right brain damage. It seems that the 3 patients with left temporo-occipital lesions who failed to benefit from imagery, although they did not show a general verbal memory deficit (*see* below), were not enough markedly to worsen the average profit which left hemisphere patients drew from imagery. Patients with Parkinson's disease and—to a lesser degree—also those with bilateral brain damage, still drew less benefit from the imagery instruction than did the other groups. This difference, however, was not sufficient to produce a significant interaction in the MANOVA.

Influence of intrahemispheric localization

The intrahemispheric localization of the lesion, as documented by the division in anterior, posterior, and other lesions, had no significant effect on visuospatial or verbal test scores in any of the three groups of patients with localized brain damage, nor were there any significant interactions in MANOVAs with the between subject factors side and intrahemispheric location of lesion. Possibly the division in anterior, posterior and other lesions was too imprecise to identify a specific influence of more particular localizations on the capacity to form mental images. From previous case reports as well as from studies of regional cerebral blood flow during imagery tasks (*see* Farah, 1984, 1988; Goldenberg, *et al.*, 1987, 1988) it could be concluded that imagery is linked to activity of visual areas in the inferior occipital and inferior temporal lobes. The CT scans of patients with localized brain damage were therefore searched for lesions which encroached on these areas. A vertical plane adjacent to the posterior end of the corpus callosum was considered as the boundary between the occipital and temporal lobes, and lesions of the basal part of the posterior brain were classified as occipital, temporal or temporo-occipital according to their situation with respect to that plane; 17

TABLE 6. PATIENTS WITH LESIONS OF THE OCCIPITAL AND OF THE INFERIOR TEMPORAL LOBE

Case	*Sex, age*	*Aetiology*	*Ab*	*Co*	*Im*	*RL*	*Wo*	*Cr*	*Pt*	*MR*	*Clinical findings*
Left hemisphere lesions											
Temporal lesions											
1 (M.G.)	M,62	Haemorrhage	2	2	7	12	54	12	29	32	Transient colour agnosia, transient hemianopia
2 (A.K.)	M,36	Astrocytoma	1	1	3	11	58	12	28	32	Anomia, verbal memory deficit
3 (W.J.)	M,33	Operated astrocytoma	1	1	0	12	57	12	32	32	Anomia, verbal memory deficit
Occipitotemporal lesions											
4(K.M.)	M,42	Ischaemia	1	2	1	11	58	12	31	32	Anomia, verbal memory deficit
5(E.D.)	F,67	Ischaemia	2	2	2	2	52	8	29	32	Pure alexia
6(W.K.)	M,28	Astrocytoma	2	0	0	7	52	9	27	28	Pure alexia
7(H.S.)	M,46	Operated astrocytoma	2	1	2	4	49	11	33	29	Transient colour agnosia, anomia, pure alexia
Occipital lesions											
8(V.T.)	M,43	Ischaemia	7	3	8	11	60	12	33	28	Hemianopia
Mean of all LBD patients			1.6	1.4	3.2	6.4	53.5	10.3	28.6	28.3	
Right hemisphere lesions											
Case	*Sex, age*	*Aetiology*	*Ab.*	*Co*	*Im*	*RL*	*Wo*	*Cr*	*Pt*	*MR*	*Clinical findings*
Temporal lesions											
9(L.A.)	M,68	Atrocytoma	1	4	8	9	58	12	24	31	Complex seizures
Occipitotemporal lesions											
10(G.H.)	M,42	Glioma	1	1	3	5	41	2	28	26	Hemianopia, heminneglect, constructional apraxia
Occipital lesions											
11(J.S.)	M,61	Ischaemia	2	2	5	9	56	10	25	30	Hemianopia
12(L.F.)	M,61	Ischaemia	2	0	5	11	56	11	28	31	Hemianopia
13(A.B.)	M,70	Ischaemia	3	3	8	11	54	12	30	32	Hemianopia, transient spatial disorientation
14(J.P.)	M,81	Haemorrhage	0	3	4	2	38	9	14	26	Hemianopia, hemineglect, constructional apraxia
15(E.W.)	F,73	Meningioma	2	3	7	0	50	11	23	31	Hemianopia
16(H.O.)	M,73	Metastasis	2	4	6	5	49	8	28	29	Hemianopia, hemineglect
Mean of all RBD patients			2.2	3.4	6.5	4.6	49.5	9.3	23.7	27.7	
Bilateral lesions											
Occipitotemporal											
17(E.V.)	M,64	Ischaemia	3	3	8	3	37	12	—	25	Left hemianopia, right upper quadrantanopia, achromatopsia apperceptive agnosia
Mean of all BBD patients			1.6	2.2	3.9	3.1	46.6	8.7	25.1	27.2	

Abbreviations as in fig. 1

patients with appropriate lesions were identified and their data are displayed in Table 6.

None of the 4 patients with left-sided temporo-occipital lesions remembered concrete words with an imagery instruction any better than abstract words, although 3 of them were able correctly to recall two pairs out of the abstract word list, which makes it unlikely that their failure to benefit from imagery was due to the severity of the general verbal memory deficit. One of them solved correctly only 8 items of the corners task and 2 of right-left, but her results on the word task were within the range of the left brain-damaged group.

There was only 1 patient with a right-sided temporo-occipital lesion. His scores on position and mental rotation were within the range of right brain-damaged patients, but he failed almost completely on corners and scored poorly on words. His result on right-left was slightly above the mean of right brain-damaged patients but during this task he spontaneously complained about difficulties in remembering what the letters looked like. Indeed, he successfully solved 2 further items after briefly being shown the respective letters. Although CT did not show evidence of a left-sided lesion, his verbal memory was also quite poor, but it improved with the imagery instruction. Case 16 with an occipital metastasis showed left-sided hemineglect not only in copying and cancellation but also in imagery (Bisiach *et al.*, 1979). When asked to describe the place of St Stephen's cathedral in the centre of Vienna as seen when standing with his back to the cathedral he mentioned only buildings to his right hand side. When asked to imagine the same place as seen when looking to the cathedral he reported the buildings he had previously omitted and omitted those he had previously reported. His results on the imagery tests, however, were within the range of right brain-damaged patients.

Case 15 had bilateral infarction in the territory of the posterior cerebral arteries which extended into the temporal lobe on the right but was smaller and restricted to the occipital lobe on the left (Goldenberg *et al.*, 1985). He could not perform the position task because he was unable to perceive more than two dots at the same time. His poor result on the word task could hence be attributed to perceptual difficulties rather than to an incapacity to form adequate mental images. In any case, he made no error on the corners task, and improved verbal memory to a perfect performance with the imagery instruction.

In sum, none of the patients with damage to secondary visual areas in the inferior occipital and temporal lobes displayed a pattern of results suggestive of a generalized inability to generate mental visual images. Patients with left temporo-occipital lesions appeared to be unable to improve their verbal memory by the use of visual imagery and the one patient with a right temporo-occipital lesion was remarkably poor in 2 of the 3 visuospatial imagery tasks. It should be noted, however, that all these patients gave a negative response to the question as to whether they themselves had noticed any change in their general ability to form mental visual images.

DISCUSSION

The purpose of the study was to find evidence for a selective impairment in the ability to form mental visual images. Data were subjected to three kinds of analysis. First, the structure of correlations between tests scores was explored by multidimensional scaling. Secondly, selective impairment in groups of patients in single tasks was sought by MANOVAs. Thirdly, patients with lesions to the inferior temporal and occipital lobes were analysed individually. From each of these approaches one relevant finding emerged. Multidimensional scaling suggested that brain damage can affect performance on visuospatial tasks that call for the formation of mental visual images differentially from those that do not; the MANOVAs showed a selective impairment of patients with Parkinson's disease in the words task which required the comparison of a mental visual image with visually perceived spatial information; individual analysis of cases suggested that patients with left occipitotemporal lesions failed to benefit from visual imagery in the memorizing of concrete nouns. These findings will now be discussed.

Correlations between tasks

The expectation that verbal and visuospatial imagery tasks share a component that makes them different from tasks that do not call for imagery was not confirmed by multidimensional scaling of correlations between test scores. The dichotomy between verbal and visuospatial task cut through the imagery tasks, suggesting a distinction between the kinds of imagery used in verbal and visuospatial tasks, respectively. It seemed, however, that brain damage can lead to a dissociation between the capacity to form visual images for the purpose of being explored visuospatially, and the capacity to explore or manipulate either imagined or perceived visuospatial information. Because of the alternative possibility of interpreting the smallest space analysis as showing an association between visuospatial imagery tasks on the one hand and all verbal memory tasks on the other, it cannot be said whether brain damage did indeed affect a distinct capacity to form the mental images that are needed for the visuospatial imagery tasks. It might be that the dissociation indicates only that brain damage can affect the general ability to retrieve information from long-term memory. In any case, there was no reliable clue as to a possible localized substrate of the capacity to form the mental visual images needed for the visuospatial tasks. If there is one, it must reside in a cerebral structure which is distributed across both hemispheres and the function of which can be affected by circumscribed lesions in either hemisphere as well as by Parkinson's disease.

Imagery in patients with Parkinson's disease

The words task differed from the remainder of the imagery tasks in that it required comparison of the mental image with a visually perceived stimulus. Both the mental visual image and the visual percept had to be attended to simultaneously. The necessity to share attentional resources would in itself be sufficient to cause interference between imagery and perception, but since both concern visuospatial information, additional modality specific interference could arise (Brooks, 1968; Podgorny and Shepard, 1978; Segal and Fusello, 1970; Baddeley, 1986).

It has been well documented that parkinsonian patients are selectively impaired in the performance of simultaneous movements (e.g., Schwab *et al.*, 1954; Benecke *et al.*, 1986; Goldenberg *et al.*, 1986). The finding that they are impaired also in a task which requires the simultaneous performance of two nonmotor activities suggests that at least parts of their motor difficulties are to be sought in the attentional control of motor performance rather than at the executive level of motor fuction. On the other hand, the similarity between motor and nonmotor impairment makes it unlikely that the enhanced vulnerability to interference in the nonmotor condition is specific to the modality of this task. The interference between visual imagery and visual perception can be explained parsimoniously by the concurrence for attentional resources and need not indicate a limited capacity in a common visual buffer.

Imagery and left occipitotemporal lesions

Patients with left occipitotemporal lesions failed to enhance their memory for words when given an imagery instruction. Although the small sample of appropriate patients prohibited statistical verification, this finding seems significant, particularly since 3 of these patients were able to remember two pairs of the more difficult abstract list. However, imagery was the only voluntary strategy that patients were instructed to use. It cannot be excluded that these patients would have been equally unable to improve their verbal memory by any other mnemotechnical strategy (Wilson, 1986). Nevertheless, the possibility that they were selectively impaired in their capacity to use imagery for verbal memory seems to merit consideration. It does not necessarily contradict Jones' (1974) finding in patients with left temporal lobectomies that these patients start from a lower level of verbal memory performance but improve as much as controls when using visual imagery. The surgical lesions were confined to the temporal lobe whereas in the present study the imagery deficit was found only in patients whose lesions affected the occipital lobe as well. The 3 patients with purely inferior temporal lesions showed either a normal improvement with imagery or a generalized verbal memory deficit that led to a floor effect.

Although the poor scores of 1 patient with a left occipitotemporal lesion on 2 of the 3 visuospatial imagery tasks are remarkable, they do not appear sufficient for diagnosing a general inability to form mental visual images. Generally, the deficit was restricted to the use of imagery in verbal memory. There is thus only partial support to Farah's conclusion from a review of reported cases of loss of imagery that left posterior lesions can lead to a generalized imagery deficit (Farah, 1984). It may be noted, however, that she reviewed only 3 cases with unilateral left-sided lesions and that in these cases the evidence for the imagery deficit was that the patients were 'unable to answer questions requiring imagery, although they did possess the ability to answer similar questions about visible stimuli and could recognize visually presented stimuli' (p. 256). Possibly, in these patients too, the imagery deficit was restricted to its use in the verbal retrieval of information from memory.

Studies of regional cerebral blood flow in healthy subjects showed enhanced activity of the left inferior occipital lobes when subjects used visual imagery to memorize word lists and when they judged the correctness of high imagery sentences such as ‘A donkey is smaller than a cow’ or ‘The green of fir trees is darker than that of grass’, but neither in subjects who judged the correctness of low imagery sentences such as ‘Austria has been a republic since 1918’ or ‘Columbus called the natives of America Indians because be believed he was in India’, nor in subjects who counted the corners of an imagined upper case letter (Goldenberg *et al.*, 1987, 1988). On the one hand these findings support the assumption that the deficits which patients with left occipitotemporal lesions display in imagery tasks are indeed specific to the imagery component of the task, on the other hand they converge with the results of the present investigation to indicate that the prominent role of this area in visual imagery does not extend to the application of imagery in visuospatial tasks.

Conclusions

The present investigation lends some support to the hypothesis that the generation of mental visual images is a distinct capability that can be specifically impaired by brain damage, but only with the qualification that the mental images needed for different kinds of tasks depend on the integrity of different brain structures.

At first sight the main distinction between the kinds of mental visual images apparently subserved by different brain mechanisms is one between images used in verbal tasks and images used in visuospatial tasks. In terms of dual coding theory this distinction could be accounted for by interactions between verbal and nonverbal systems and consecutive functional subdivisions of the nonverbal system into a region specialized for visuospatial processing and another responsible for providing mental visual images to verbal memory (Paivio and Te Linde, 1982; Paivio, 1986). Models which assume that there are specialized processors that construct the mental visual image out of information stored in long-term memory and display it in a visual buffer (Kosslyn, 1983, 1987; Farah, 1984) would have to be expanded to allow for two sets of ‘imagery devices’, one being active in visuospatial, the other one in verbal imagery tasks.

Before concluding that the cerebral basis of mental visual imagery depends only on the verbal or visuospatial nature of the task for which the image is needed, it seems worthwhile to consider in more detail the differences between the verbal and visuospatial imagery tasks administered in the present study. They differed not only in the modality of the treatment to which the mental images were subjected, but also in the informational content of the mental images. The verbal imagery tasks required imagining of the appearance of objects, whereas in the visuospatial tasks images of letters or words had to be formed. Thus the visuospatial imagery tasks concerned images of verbal material and the verbal tasks images of nonverbal information. Presumably this difference will hardly account for the predominant role of the left-sided occipitotemporal region in the verbal imagery tasks.

There are other differences between mental images of objects and of letters. Both kinds of images have a 'descriptive' component in that they describe visual perceptions and present knowledge that is also used for the perceptual indentification of the respective items. Images of letters have a 'prescriptive' component too: they depict information that controls the motor action of writing. Dissociation of these two aspects of the knowledge of written language is the hallmark of alexia without agraphia which is typically caused by left occipitotemporal lesions (Benson, 1985). In the present study several patients with pure alexia were examined and showed normal performance on the visuospatial imagery tasks. Patients who could not write down the letters on dictation were excluded from examination. It may well be that these patients who without exception had left hemisphere lesions would have been equally unable to imagine the letters and hence to solve the visuospatial imagery tasks. Since motor plans may be stored in memory in terms of their spatial features rather than as a collection of motor actions (Smyth, 1984), the distinction between visual and motor images may ultimately refer to one between modality specific visual and supramodal spatial information (Levine *et al.*, 1985; Farah *et al.*, 1989).

On the one hand, the information necessary to form the mental image of a letter can thus be retrieved from motor memory in addition to being retrieved from visual memory. On the other hand, imagining of letters demands retrieval of less information than imagining of objects. There are only 26 capital letters and they are composed out of a very limited number of elements. Although there is no limit to the number of differences between the visual appearances of different types of writing the tests clearly favoured the imagining of prototypical letters which show only those features that are common to all particular writings of a letter. In any case, such a reduced image was largely sufficient to solve the visuospatial imagery tasks. In the words task a distinct type of letter had to be imagined, but since the features of this type were described in an explicit verbal instruction, subjects could easily reconstruct them during the comparison between image and percept out of the retrieved image of a prototype which showed only basic features of the letter. Besides, even in this task the specifications concerned only the symmetry and the boldness of the letter and there was no need to imagine additional features such as colour, surface structure, exact boundaries of the bars or decorative accessoires characterizing a certain type of writing. There is no reason to believe that prototypical images of objects would not be efficient for enhancing memory for their names, but as soon as both kinds of images are reduced to images of prototypical instances it becomes clear that letters are a highly uniform class of visual appearances which can be reconstructed from a very restricted amount of knowledge whereas the possible number of basic objects (Rosch *et al.*, 1976) is virtually indefinite and there are few if any structural elements common to all of them (Hoffman and Richards, 1984).

It thus may be that the neurological basis of mental visual imagery varies with the content of the image rather than with the modality of the task for which it is used. It remains open whether the amount of information contained in the image is crucial or whether it is a certain qualitative aspect of information that determines the cerebral localization of visual imagery.

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EVIDENCE FOR PRESERVED READING IN 'PURE ALEXIA'

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SUMMARY

We describe 4 patients who developed pure alexia after infarctions of the left cerebral hemisphere. All subjects employed a letter-by-letter strategy (with varying degrees of success) to explicitly identify visually presented words. Although all 4 subjects explicitly denied that they could identify briefly presented words, they all performed significantly better than chance on lexical decision and forced-choice semantic categorization tasks with briefly presented words which they could not explicitly identify. Three subjects regained the ability to explicitly identify briefly presented words; these subjects were more accurate with nouns than functors and words of high as compared with low imageability. Additionally, these subjects were impaired in the processing of suffixes. These data are not accommodated by the 'disconnection' account of pure alexia but are more consistent with the hypothesis that reading in these patients is mediated by the right hemisphere.

INTRODUCTION

In his seminal contributions to the study of acquired dyslexia, Dejerine (1891, 1892) described 2 patients with reading impairment in association with lesions of the left cerebral hemisphere. The first patient (Dejerine, 1891), who had suffered an infarction involving the angular gyrus, was noted to be both alexic and agraphic; the second (Dejerine, 1892) developed alexia without agraphia or significant aphasia in association with infarction of the left medial occipital cortex, periventricular white matter of the left occipital lobe and small portions of the splenium of the corpus callosum. In light of these findings, he proposed that the left angular gyrus contained the word forms or 'optical images of letters' critical for word recognition and writing. Thus alexia with agraphia was attributed to a destruction of the stored word forms; alexia without agraphia or 'pure' alexia, in contrast, was attributed to a disconnection of the visual verbal information in the right hemisphere from the preserved word forms in the left angular gyrus.

Over the years, numerous investigators have confirmed Dejerine's original clinical description (e.g., Bastian, 1898; Foix and Hillemand, 1925). Additionally, although a number of different pathological substrates for the syndrome have been described (e.g., left lateral occipital damage (Damasio and Damasio, 1983);

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a white matter lesion undercutting the left angular gyrus (Greenblatt, 1976)), in virtually every instance the findings have been consistent with Dejerine's disconnection hypothesis in that the lesion severed white matter tracts connecting the preserved right occipital lobe and the left angular gyrus. Lastly, a number of careful investigations of the neuropsychological deficit underlying pure alexia have provided data interpretable within the disconnection framework (e.g., Warrington and Shallice, 1980; Patterson and Kay, 1982). Thus because of the apparent consistency of the clinical, pathological and neuropsychological findings, Dejerine's anatomically based account of the syndrome of pure alexia has remained the most widely accepted explanation of the syndrome.

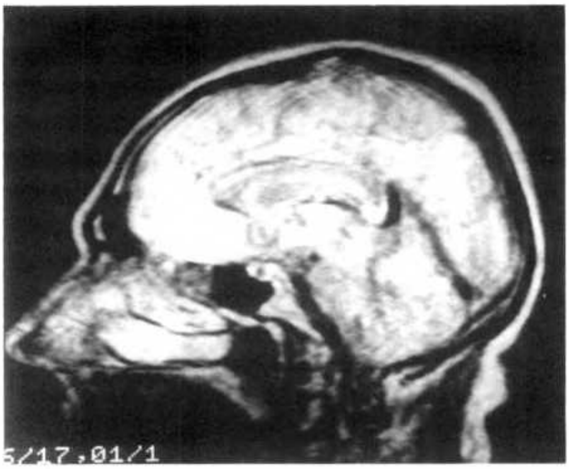
Recently, however, a number of patients with pure alexia have been demonstrated to have certain capacities which appear to be inconsistent with the traditional disconnection account of pure alexia. Caplan and Hedley-White (1974), for example, described a patient with pure alexia who, although apparently unable to identify words explicitly, could distinguish real words from nonword letter strings. Additionally, several patients have shown the ability to match written words which they were unable to read aloud to objects (Landis *et al.*, 1980) or to auditorily presented words (Kreindler and Ionăşescu, 1961; Grossi *et al.*, 1984). Finally, Shallice and Saffran (1986) reported a patient who was unable to explicitly identify stimuli presented for approximately 2 s and yet could distinguish words from non-words and performed better than chance on certain forced-choice word categorization tasks.

We report data from 4 subjects with pure alexia who, despite their explicit claims to the contrary, were able to distinguish words from nonwords and to derive semantic information from rapidly presented written words which they could not identify. These data are inconsistent with Dejerine's attribution of pure alexia to a disconnection of the literate left hemisphere from visual verbal information restricted to an illiterate right hemisphere. Although there are alternative possibilities, these data provide support for the claim that the right hemisphere is literate (Coltheart, 1983; Zaidel, 1978; Saffran *et al.*, 1980).

SUBJECTS

Case 1

J.G. is a 53-yr-old right-handed meat salesman with a high school education who noted the sudden onset of an inability to read road signs and an inability to see to the right while driving. No weakness was noted and he drove home uneventfully. As his symptoms persisted and he noted that he was unable to remember commonly used telephone numbers, he sought medical attention the next day. Examination on admission revealed a dense right homonymous hemianopia, short-term memory impairment, moderate anomia and profound alexia. CT and magnetic resonance imaging (MRI) scans demonstrated small areas of infarction involving the left lateral geniculate and/or the optic radiation and the splenium of the corpus callosum (*see* figs 1, 2). Although the MRI scan demonstrated an equivocal small left frontal infarct, the occipital, temporal and parietal cortex was normal.



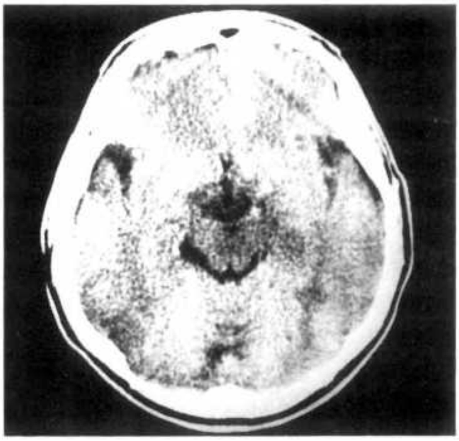


FIG. 1 (*left*). Midsagittal MRI section from *Case 1* demonstrating a lesion of the splenium of the corpus callosum. FIG. 2 (*right*). Axial MRI section from *Case 1* demonstrating a lesion in the region of the lateral geniculate nucleus on the left.

When first examined by the present investigators approximately 7 wks after the stroke, the patient manifested a right homonymous hemianopia but no other elementary sensory deficits. Language testing with the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1972) revealed no aphasia although a mild naming impairment was evident on the Boston Naming Test (Goodglass *et al.*, 1983); he correctly identified 48 of 60 items (5 with a phonological cue). Even when unable to name the item depicted by the line drawing, he typically provided some appropriate information (e.g. 'palette'→'something to do with artists, you draw from it'). There was no suggestion of a visual agnosia. He named and pointed to named colours normally.

The patient's writing of single words was thought to be consistent with his level of education. He correctly wrote 38 of 40 regular and 35 of 40 irregular words matched for length and frequency. Errors tended to involve single letter substitutions and to preserve phonology; for example, 'subtle' was written as 'suttle' and 'niche' as 'nitch'. He correctly wrote 14 of 15 nonwords. Spelling aloud and naming of spelled words were also at least relatively normal. He correctly named 35 of 40 regular and 34 of 40 irregular words spelled aloud by the examiner. Most errors were word substitutions in which the initial portion of the letter string was preserved (e.g., 'colonel'→'colonial').

The subject's naming of letters was slow and imperfect; he correctly identified 23 of 26 lower case letters presented individually but often required multiple attempts before arriving at the correct name. When asked to identify letters in words, he erred on approximately 20% of trials. He rapidly and accurately identified 10 ideograms such as '$', '&' and '%'. He identified written numbers rapidly but imperfectly; he correctly identified 5 single digit numbers, 5 two-digit numbers but only 4 of 5 three-digit numbers.

The patient stated that he was unable to read except by using an explicit letter-by-letter strategy; using this strategy, his performance was not affected by the regularity of print-to-sound correspondences, part of speech or imagery. He correctly 'read' 35 of 39 irregular words and 36 of 39 regular words matched for length and frequency; he identified 28 of 30 nouns and 27 of 30 functors matched for length and frequency. Most errors were attributable to letter misidentifications; for example, he read 'match' as 'march' and 'marker' as 'market'. He read 30 of 40 nonwords correctly; all 10 errors were attributable to grapheme misidentifications.

Both the speed and accuracy of the patient's reading were influenced by word length. The mean time required to correctly identify each of 20 words of 3, 4, 5, 6 or 7 letters is presented in Table 1; also presented is the number of words incorrectly identified.

TABLE 1. SPEED OF ORAL READING AS A FUNCTION OF WORD LENGTH*

	No. of letters				
Case	*3*	*4*	*5*	*6*	*7*
1 (J.G.)	9(10)	12.7(10)	17.1(8)	27.1(10)	28.1(8)
2 (T.L.)	2.4(10)	2.9(10)	3.4(10)	4.9(10)	4.4(10)
3 (J.C.)	2.4(10)	5.9(8)	17.2(9)	16.4(9)	29.8(9)
4 (A.F.)	31(2)	83(1)	—	—	—

* In seconds; number correct in parentheses.

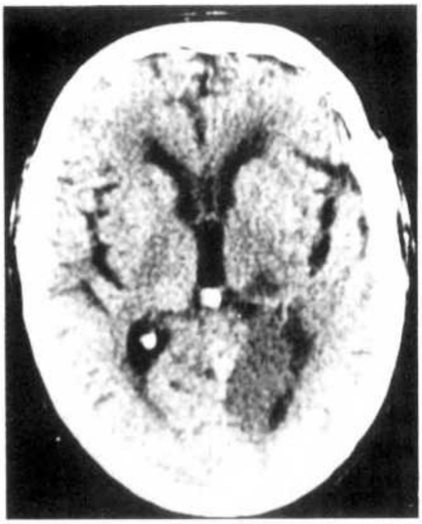
J.G. was tested over a period of approximately 8 months. Although the initial clinical examination and formal visual fields revealed a dense right homonymous hemianopia, approximately 3 months after his infarction he noted the return of some vision in the right visual field; J.G. stated that he could detect movement and was aware of 'outlines' or silhouettes in the impaired visual field but could not identify words, letters or small objects on the right. The possible implications of this partial recovery of vision for the subject's reading was extensively tested; a Gerbrands four-field tachistoscope and Apple IIe microcomputer were used to present letter strings (both vertically and horizontally arrayed) for intervals varying from 50 to 150 ms in each visual field. Although he performed significantly above chance on a lexical decision test with stimuli presented in the left visual field (approximately 85% correct), J.G. consistently performed at chance (and never explicitly identified words) with stimuli presented in the right visual field. Thus there was no evidence that the return of vision in the right visual field had any implications for his performance on the reading tests described below.

Case 2

T.L. was an 85-yr-old male, a former bookkeeper, who noted the sudden onset of clumsiness of the right hand and leg and loss of vision on the right while walking. The initial neurological examination revealed a dense right homonymous hemianopia and minimal right-sided weakness; the weakness resolved within 24 h. A CT scan demonstrated a large left occipital infarct involving the forceps major on the left (*see* figs 3, 4).

When first seen by one of the present investigators (H.B.C.) 10 days after his stroke, he showed a dense right homonymous hemianopia but no other sensory or motor disturbance. Speech and naming as assessed by the BDAE were normal. Spelling aloud and naming of spelled words were normal; performance was not affected by regularity of print-to-sound correspondences, imagery or part of speech.

T.L. identified 23 of 26 single letters but often required multiple attempts. He identified 10 out of 10 symbols and 14 of 15 numbers correctly. He misnamed 3 of 10 colours but matched colour patches flawlessly. He appeared to be unable to read except by using an explicit letter-by-letter strategy. Using this strategy, he demonstrated no effect of linguistic factors such as imagery or part of speech but his speed and, to a lesser extent, accuracy, were clearly affected by word length. The average time required to correctly read words of varying length is shown in Table 1. The data reported here were obtained over a 3 wk interval.



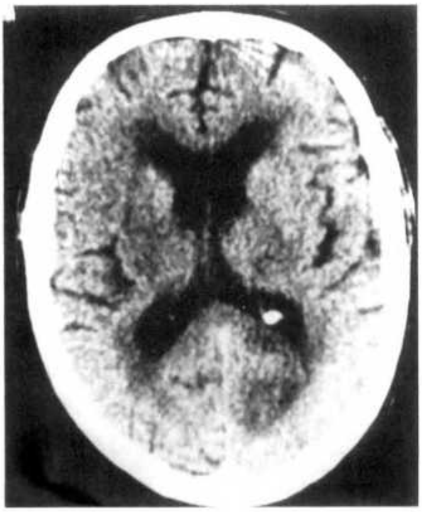


FIG. 3 (*left*). Low ventricular CT scan section from *Case 2* demonstrating infarction of the left inferior occipital lobe. FIG. 4 (*right*). CT scan from *Case 2* demonstrating infarction of the left midoccipital lobe.

Case 3

J.C. was a 26-yr-old female high school graduate who noted the sudden onset of a right hemiplegia, right hemisensory loss and right homonymous hemianopia. A CT scan performed 2 wks later demonstrated a large infarct involving the bulk of the left occipital lobe including the forceps major and extending into the posterior limb of the internal capsule.

When first examined 2 months after her stroke, she manifested a dense right homonymous hemianopia and right hemiparesis. Spontaneous speech was normal and formal language testing with the BDAE demonstrated no aphasia. She correctly spelled aloud 26 of 30 regular and 26 of 30 irregular words as well as 20 of 20 functors. Most errors involved the omission or substitution of a single letter (e.g., 'pitiful' → 'pitaful'). On another occasion she was asked to name the same corpus of words spelled aloud by the examiner; she correctly identified 30 of 30 regular words, 28 of 30 irregular words and 19 of 20 functors.

Initially, her writing was abnormal. When asked to write single letters to dictation she correctly wrote 25 of 26 letters with her left hand; however this task required 22 min. Writing of words was characterized by very frequent letter substitution errors which she frequently recognized but was unable to correct despite the ability to name the letter she was attempting to produce; when asked to write the word 'idea', for example, she wrote 'hiem' while correctly spelling the word aloud. She did not improve with anagram letters. She correctly identified 7 of 10 ideograms and read 5 of 5 one-digit, 4 of 5 two-digit and 1 of 5 three-digit numbers. She named colours correctly.

J.C. named 21 of 26 letters correctly but this process was quite slow and she frequently produced a series of incorrect letter names before finding the correct name. She was unable to read aloud any words on sight and attempted to read using an explicit letter-by-letter strategy. Initially, this strategy was ineffective because of frequent letter misidentifications; after approximately 1 month, however, she had improved to the point at which she read 25 of 30 regular and 24 of 30 irregular words as well as 19 of 20 functors using a letter-by-letter strategy. Using this technique, her performance was affected by word length but not by imagery or part of speech (*see* Table 1). She was examined over a 2½ month interval.

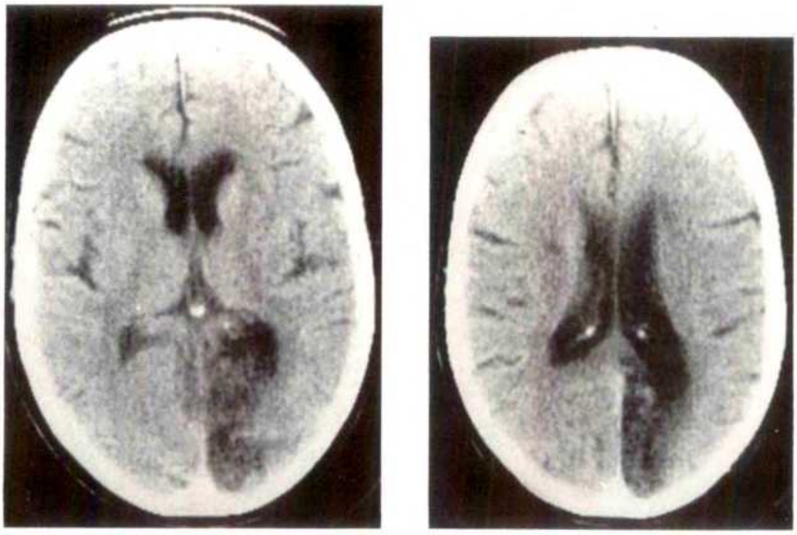


FIG. 5 (*left*). Low ventricular CT scan from *Case 4* demonstrating infarction in the left occipital lobe. FIG. 6 (*right*). High ventricular CT scan from *Case 4* demonstrating infarction in the left occipital lobe.

Case 4

A.F. was a 75-yr-old woman with a high school education who developed pure alexia and visual agnosia after a coronary artery bypass graft operation. Although no intraoperative complication was noted, she was slow to regain consciousness. On waking 3 days after the operation she was found to have a dense right homonymous hemianopia and was thought to be unable to recognize visually presented stimuli including faces, objects and words; she identified family members only by voice. An EEG revealed bilateral posterior slowing; a CT scan performed 1 wk after the operation revealed an infarct which involved the left medial occipital cortex and the forceps major (*see* figs 5, 6).

When examined approximately 4 months after her stroke, she was noted to have a minimal right hemiparesis, a dense right homonymous hemianopia and a moderately severe object agnosia. She was not prosopagnosic. Her spontaneous speech was normal and formal testing with the BDAE revealed no deficits that could not be attributed to her visual recognition impairment. She identified only 3 of 10 ideograms. Colour naming appeared to be normal.

Formal testing of her visual recognition impairment suggested that most errors on tests of visual naming were misidentifications based on specific visual features (e.g., wheelchair→'a wagon with wheels'). She performed at chance (43/80 correct) on a forced choice task in which she was required to distinguish real objects from non-objects. She performed normally (43/44 correct), however, on a task in which she was forced to indicate if two irregular, unfamiliar shapes were identical. These results suggest that her deficit is at the level of matching visual information to stored object images or representations.

A.F. correctly spelled aloud 27 of 30 regular, 28 of 30 irregular words and 18 of 20 functors. On a different occasion she was asked to name the same words when spelled aloud by the examiner. She correctly identified 26 of 30 regular words, 27 of 30 irregular words, and 19 of 20 functors. Her writing of single words to dictation was quite similar to her oral spelling. She named single letters accurately (24/26) but slowly with frequent self-corrections. When asked to read words aloud she attempted to use a letter-by-letter strategy. Because of frequent letter misidentifications, however, this strategy was extremely slow and imprecise. She identified only 3 of 10 three-letter words and 1 of 10 four-letter words. She was unable to identify any of the five, six, or seven-letter words included in the test assessing the effect of word length. She occasionally identified words of 5 or more letters using a letter-by-letter strategy; however, she typically appeared to be guessing on the basis of partial letter information. A.F. was tested over a 3 month interval during which time there was little apparent change in her visual agnosia.

EXPERIMENTAL INVESTIGATIONS

The investigations reported below are motivated by an information processing model which distinguishes a number of distinct processes in reading. First, the stimulus letter string is compared with entries in a stored catalogue of familiar words; if the stimulus corresponds to an entry in the 'visual lexicon', the meaning of the word may be established by accessing the appropriate information in the semantic system. Finally, oral reading (at least for words with irregular print-to-sound correspondences) requires the activation of the entry in the 'phonological output lexicon' or listing of the phonology corresponding to a familiar word. Although a full discussion of these information processing accounts of reading is beyond the scope of this paper, it should be noted that one important consequence of the distinction between the different processing modules is that a reading impairment may be caused by a variety of processing deficits. In the context of these models, therefore, it is important to attempt to define the level(s) of processing at which reading may be affected.

The following experiments were undertaken to assess the integrity of the processing components described above. First, lexical decision tests were performed to determine whether subjects could access stored entries in the visual input lexicon; on this task subjects were asked only to indicate if a letter string was a real word or not. Secondly, a variety of forced-choice categorization and picture-matching tasks were performed to assess the patients' ability to access (at least a portion of) semantic information appropriate to a stimulus. Lastly, the ability to read aloud was investigated; this task differs from the previous tasks in that it may also require access to stored phonological information.

Lexical decision test

Although all subjects denied that they were able to identify words without using a letter-by-letter strategy, a lexical decision test was administered to investigate the possibility that words were being processed without awareness. The ability to discriminate between words and nonword letter strings would suggest that subjects were able to access a catalogue of stored word entries.

Methods. A total of 240 letter strings was presented to each subject; stimuli included 60 high frequency words (mean frequency of 445.8 counts per million; Kucera and Francis, 1967), 60 low frequency words (all 1 count per million), 60 'wordlike' nonwords such as 'shart' (mean 'N' of 10.9; Coltheart *et al.*, 1977) and 60 nonwords with unusual or illegal orthographic sequences such as 'twilk' (mean 'N' of 1.3). Letter strings were unaffixed and varied in length from 3 to 5 letters.

Stimuli in these four experimental conditions were matched for length and presented in random sequence with an Apple 2e and green screen monitor or Apple MacIntosh microcomputer using software which permitted the stimulus duration to be controlled.

For each trial, pressing the spacebar on the keyboard caused a centrally placed fixation point to be replaced by a letter string which persisted for the preprogrammed interval; there was no poststimulus mask. Subjects were instructed to depress a response key on the right if the stimulus was a word or a key on the left for a nonword. Reaction times were measured from the onset of the stimulus to the response. A block of 42 practice trials with feedback about response accuracy was presented before the 240 item test. For all subjects, presentation times were set to be substantially shorter than those required for explicit identification by a letter-by-letter strategy. A stimulus duration of 250 ms was used for Cases 1, 3 and 4; for Case 2 who was most adept at the use of the letter-by-letter strategy, an exposure time of 150 ms was used.

Subjects were told that it was not necessary to identify the stimulus explicitly, but simply to indicate if the letter string was a word; subjects were also told to report any letter string which they believed that they had recognized. As all subjects initially continued to try to identify the constituent letters explicitly, they were repeatedly urged to attempt to derive a 'feeling' for or 'impression' about the letter string and to guess if they were uncertain.

Results. Because of the possibly confounding effects of the left hemisphere lesions on the reaction times of the right hand, only data on response accuracy was formally analysed. The results for each subject, expressed as the percentage of stimuli considered to be real words (percentage of 'yes' responses), are presented in Table 2. All subjects performed better with high as compared to low frequency words and Lo-N as compared to Hi-N nonwords. Differing response biases appeared to lead to some variability in response to low frequency words and Hi-N nonwords. Case 1, for example, tended to reject letter strings about which he was uncertain while Case 2 tended to accept low frequency words and Hi-N nonwords. On rare occasions, subjects correctly identified a stimulus word; no subject identified more than 4 (3.4%) words. Case 2 misidentified two Hi-N nonwords, reporting 'tarch' as 'tape' and 'solt' as 'sole'.

To determine whether subjects differentiated words from nonwords reliably, a bias-free statistic derived from signal detection theory, 'd' was calculated for each

TABLE 2. LEXICAL DECISION TEST*

	Words			*Nonwords*		
Case	*Hi F*	*Lo F*	*Hi+Lo*	*Hi N*	*Lo N*	*Hi+Lo*
Pure alexics						
1	75	37	56	35	25	30
2	82	78	80	63	38	50
3	78	52	65	28	11	19
4	80	53	67	42	18	30
Deep dyslexics						
P.J.	90	52	71	23	7	15
A.T.	93	43	68	15	7	11

* % 'yes' responses.

subject; for Cases 1-4, d′ was 0.675, 0.842, 1.30, and 0.964, respectively. In all instances, subsequent analysis with a Z statistic revealed that the d′ values were significantly greater than would be expected by chance (Z = 4.06, 4.85, 7.36 and 5.72, respectively, all $P < 0.05$)

The lexical decision test described above was also administered to 2 subjects with 'deep' dyslexia who correctly read aloud approximately 80% of concrete nouns; as indicated in Table 2, although both subjects were more accurate than the pure dyslexics, they manifested the same pattern of performance.

TABLE 3. PERFORMANCE ON LEXICAL DECISION TEST AS FUNCTION OF LENGTH*

	No. of letters					
Cases	*Hi F*			*Lo F*		
Words	*3 (n = 8)*	*4 (32)*	*5 (20)*	*3 (9)*	*4 (29)*	*5 (22)*
1	75	69	85	67	31	32
2	75	91	70	78	79	77
3	63	84	75	55	52	50
	Hi N			*Lo N*		
Nonwords	*3 (8)*	*4 (32)*	*5 (20)*	*3 (9)*	*4 (30)*	*5 (21)*
1	25	41	30	22	33	19
2	37	78	50	33	47	28
3	37	28	25	22	7	10

* % 'yes' responses.

The effect of word length on performance was also investigated. For each subject, the percentage of correct responses for high and low frequency words and Hi N and Lo N nonwords of 3, 4 and 5 letters is expressed in Table 3. Unfortunately, these data are not available for Case 4. Although the range of letter string lengths is small, no subject demonstrated a significant effect of word length for any of the four types of stimuli.

Two additional post hoc analyses were performed to investigate the contribution of sublexical factors such as the familiarity of letter arrays. First, performance with words and nonwords matched for 'N' was assessed; if responses on the lexical decision test were determined by the familiarity of letter strings rather than lexical information, it would be predicted that performance with words and nonwords matched for sublexical orthographic familiarity would not differ. Stimuli for this post hoc comparison included the 60 high (mean 'N' of 10.9) and 6 low 'N' nonwords (mean 1.3) as well as 40 (20 high and 20 low frequency) Hi-N words (mean of 10.3) and 40 (20 high and 20 low frequency) Lo-N words (mean of 1.7). The data for Cases 1-3, expressed as the percentage of stimuli judged to be a word, are presented in Table 4. Data for Case 4 were not available. For both Lo-N and Hi-N stimuli, all subjects accepted a significantly greater ($\chi^2 \geqslant 4.28$, $P < 0.05$) proportion of words as compared to nonwords.

TABLE 4. PERFORMANCE ON LEXICAL DECISION TEST AS FUNCTION OF 'N'*

	Case		
	1	*2*	*3*
Hi N			
Words	63	83	75
Nonwords	33	63	28
Lo N			
Words	55	75	60
Nonwords	28	38	13

* % 'yes' responses.

In the second analysis, the role of sublexical orthographic similarity was assessed by comparing the performance of Cases 1–3 with high and low-frequency words matched for N count. Normal subjects, whose performance is thought to reflect the influence of lexical information, respond more accurately and quickly to high as compared with low-frequency words on lexical decision tests (Forster, 1976); if these patients also base their responses on lexical information rather than sublexical information, it might be expected that they would respond more reliably to high as compared to low-frequency words matched for N count. Stimuli for this post hoc comparison included 47 high and 47 low-frequency words matched for N count (mean of 5.7 ± 4.2 and 5.8 ± 4.0, respectively). All subjects correctly accepted a larger proportion of the high as compared to low-frequency words; for Cases 1 and 3 the difference was highly significant (70% vs 40% for Case 1, 83% vs 47% for Case 3; both $P < 0.01$ using a χ^2 test); for Case 2 the difference was not significant (79% vs 68%).

For 2 subjects (Cases 1 and 4), performance on a lexical decision test as a function of exposure time was investigated. For Case 1, the lexical decision test described above was repeated on a number of occasions. Initially, 100 of the 240 stimuli described above were presented using an Apple 2e and a program which sustained stimulus presentation until the subject responded. On this occasion, the test was terminated after 100 items for lack of time; Case 1 required 90 min to complete 100 items. As indicated in Table 4, he responded correctly to 86% of words and 92% of nonwords with unlimited time. Subsequently, the full 240 item test was administered with exposure durations of 50 ms, 250 ms, 500 ms and 2000 ms; all administrations were performed at least 1 wk apart during the first 6 wks of the subject's evaluation; with each administration, the stimulus sequence was rerandomized. On no occasion did the subject explicitly identify more than 4 of the stimuli. Case 1 was not given feedback regarding the accuracy of his individual responses, although he was told that in general he was doing well. As indicated in Table 5, d′ was calculated for each administration. Analysis with the Z statistic revealed that performance was significantly above chance at each exposure time except 2 s.

For Case 4, a different lexical decision test was administered on two occasions; stimuli included 40 words of high imagery (all rated > 5.0 (Paivio *et al.*, 1968) and high frequency (all > 100 counts per million (Kucera and Francis, 1967)) and 40 nonwords derived from high frequency, high imagery words by changing 1 letter; with a 2 s exposure, she performed at chance (54% correct); with a 250 ms exposure, however, her performance was significantly better than chance (74% correct, $\chi^2 = 18.1$, df = 1, $P < 0.001$).

TABLE 5. LEXICAL DECISION TEST AS FUNCTION OF EXPOSURE DURATION IN CASE 1*

	50 ms	*250 ms*	*500 ms*	*2000 ms*	*Unlimited*
Words	49%	59%	55%	51%	86%
Hi F	57	68	70	64	
Lo F	40	57	40	37	
Nonwords	22%	36%	21%	54%	8%
Hi N	27	33	25	68	
Lo N	18	28	18	40	
d′	0.75	0.72	0.93	0.13	2.49
Z	4.36	4.40	5.38	0.775	7.32

* % 'yes' responses.

Although necessarily subjective and anecdotal, the subjects' comments about the test were informative. On most trials, subjects claimed to have 'seen' only 1 letter or insisted that the stimulus had been too fast and that they had seen 'nothing'. Without exception, subjects insisted that they were guessing throughout the test and reacted with surprise and consternation to the news that they had performed significantly better than chance.

Discussion. The fact that subjects discriminated (albeit imperfectly) between words and nonwords on a lexical decision test in which stimuli were presented too briefly to permit explicit word recognition suggests that they were able to derive information about the visual form of the stimulus letter string despite their statements to the contrary. This ability is unlikely to be attributable to the familiarity of sublexical letter strings. Post hoc analyses in which an attempt was made to control for the familiarity of sublexical orthographic units by matching stimuli in 'N' count (Coltheart *et al.*, 1977) suggest that the subjects are not relying on sublexical information but presumably are accessing lexical information. Finally, it might be expected that word length would influence performance significantly if the subjects were responding on the basis of the familiarity of sublexical components of the visual array; the subjects with pure alexia, like normal readers (Frederiksen and Kroll, 1976; Schiepers, 1980) were not substantially affected by word length. This finding also argues strongly against the alternative hypothesis that subjects were using a strategy of rapid letter identification and 'piecing' the word together using serial letter information; if a letter-by-letter strategy were being used, a clear effect of word length should have emerged in these subjects who demonstrated difficulties even in the identification of single letters.

The finding that Cases 1 and 4 performed *better* with stimuli presented for 250 ms as compared with 2000 ms further argues that the performance with rapid presentation was not mediated by serial letter identification. These data, in conjunction with the observation that at least one of the subjects (Case 1) used an explicit letter-by-letter strategy with stimuli presented for 2000 ms but not for 250 ms raises the possibility that differences in performance with different exposure times reflect the use of different strategies (Landis *et al.*, 1980; Shallice and Saffran, 1986).

Word comprehension

In the light of the previous results suggesting that all 4 subjects were able to access orthographic information about words which they could not explicitly identify, a series of investigations was undertaken to determine if these subjects were also able to access semantic information in the absence of explicit word identification.

Word categorization

1. Animal names

Methods. In the first experiment, subject were asked to indicate whether a rapidly presented word was an animal name. Stimuli consisted of 25 animal names (e.g., 'mouse'), 25 words judged to be visually similar to the animal names (e.g., 'mount'), and 25 words judged not to be visually or phonologically similar to the animal names (e.g., 'rally'). Visually similar foils shared at least the first 2 letters with the matched animal name. The three types of stimuli were matched for frequency; mean frequencies for the animal names, visually similar foils and unrelated foils were 12.6 ± 23.58, 13.56 ± 22.1, and 12.72 ± 23.93 counts per million (Kucera and Francis, 1967), respectively. Animal names and foils differed in length by no more than 1 letter; mean letter lengths for the animal names; visually similar foils and unrelated foils were 5.96 ± 1.0, 5.92 ± 0.93, and 5.96 ± 1.0, respectively. Stimuli were presented with an Apple 2e or MacIntosh microcomputer using exposure times as indicated in Table 5. Subjects were instructed to say 'yes' if the word was the name of an animal.

For this and other tests of comprehension, subjects were encouraged to attempt to derive a 'feeling' or 'impression' from the word and *not* simply to identify letters. Emphasis was placed on the importance of the category judgement, not explicit word identification; subjects were asked, however, to inform the investigator whenever they believed that they had recognized a word. Subjects were not told the proportion of stimuli which were animal names and were not given feedback regarding the accuracy of their individual responses.

Results. Data, expressed as percentage correct, are expressed in Table 6. Statistical analysis using a $3 \times 2\chi^2$ demonstrated that all subjects were able to

TABLE 6. ANIMAL NAMES—CATEGORIZATION*

Case	*Animal*	*Visual foil*	*Unrelated foil*	*Total*
1 (0.25 s)	80	72	72	75
2 (0.1 s)	96	52	60	69
3 (0.25 s)	68	92	96	85
4 (0.25 s)	80	60	72	71

* % correct.

TABLE 7. ANIMAL NAMES—EXPLICIT RESPONSES*

	Case			
Response category	*1*	*2*	*3*	*4*
Correctly named	1.3	2.6	6.7	0
Incorrectly named	2.7	1.3	6.7	7.9
Unrelated	2.7	1.3	2.7	5.3
Within category substitutions	0	0	4.0	2.7
Partial semantic information	0	0	0	1.3

* % of trials.

distinguish animal names from other words (2 df, $P < 0.01$ for all subjects). As we were concerned with our subjects' ability to categorize words which they could not identify explicitly, a second analysis was performed in which explicitly identified stimuli were excluded; the results of this analysis do not differ significantly from those noted above.

Subjects offered explicit responses to a relatively small number of stimuli. The percentage of stimuli correctly identified and misnamed is presented in Table 7. All word misidentifications were further categorized as within category substitutions ('tiger'→'lion') or semantically unrelated substitutions; most of the latter errors appeared to be visually based (e.g., 'hotel'→'honour'). All but one of the within category substitutions also involved the production of visually similar words. Only stimuli from the target category produced semantically related substitutions. On one occasion Case 4 was unable to report the specific word but offered partial semantic information (e.g., 'rabbit'→'an animal with big teeth').

2. *Food names*

Methods. A second similar forced-choice categorization experiment was performed in which subjects were asked to indicate whether the referent of a rapidly presented word was edible. Stimuli consisted of 25 food items (e.g., 'grape'), 25 visual foils (e.g., 'graph') and 25 unrelated words (e.g., 'truck'); the three groups of stimuli did not differ in mean frequency (15.0±15.53, 25.0±55.4, 15.0±15.52 counts per million (Kucera and Francis, 1967), respectively ($t = 0.87$, ns), or length (mean letter length 5.76±1.03, 5.84±0.97, 5.76±1.03, respectively). Stimuli were presented with an Apple 2e or MacIntosh microcomputer using exposure times as indicated in Table 8. Subjects were instructed to say 'yes' if the rapidly presented word designated a type of food.

TABLE 8. FOOD NAMES—CATEGORIZATION*

Case	*Foods*	*Visual foil*	*Unrelated foil*	*Total*
1 (0.25 s)	84	76	80	80
2 (0.1 s)	76	56	68	67
3 (0.25 s)	72	72	92	79
4 (0.25 s)	76	68	84	76

* % correct.

TABLE 9. MALE/FEMALE NAMES—CATEGORIZATION*

Case	*Male*	*Female*	*Total*
1 (0.25 s)	74	76	75
2 (0.1 s)	66	74	70
3 (0.25 s)	72	70	71
4 (0.25 s)	84	76	80

* % correct.

Results. Results, expressed as percentage correct, are expressed in Table 8. Once again a $3 \times 2\chi^2$ analysis was performed; all subjects were able to distinguish animal names from other words (2 df, $P < 0.01$ for all subjects). Elimination of those stimuli to which subjects offered an explicit response did not substantially alter the results.

All explicit verbal responses were recorded and categorized as described above; the results of this analysis were similar to those presented in Table 6.

3. *Proper names*

Methods. In this experiment subjects were asked to judge whether rapidly presented proper names were appropriate for men or women. Stimuli for this test included a randomized list of 50 male and 50 female names varying in length from 3 to 8 letters; mean letter length was 5.82 ± 1.21 for men's and 5.78 ± 1.27 for women's names. Thirty-four of the 50 pairs of male and female names contained the same first 3 letters (e.g., 'Maurice' vs 'Maureen') or differed by only one letter (e.g., 'John' vs 'Joan'). Subjects were told that all stimuli were proper names and were asked to indicate whether the name was appropriate for a man or for a woman. Stimuli were presented with the apparatus described above using exposure times as indicated in Table 9.

Results. The data, expressed as percentage correct, are expressed in Table 9. A χ^2 analysis demonstrated that all subjects categorized the proper names significantly better than chance (1 df, $P < 0.005$ for all subjects). As before, eliminating the explicitly identified items from the analysis did not significantly alter the results of the analysis. Additionally, it should be noted that 11 of the female but none of the male names ended in the letter 'a'; eliminating these names from the data did not effect the outcome of the statistical analysis. Finally, all subjects performed significantly above chance on the 34 pairs of names matched for the first 3 letters or differing by only 1 letter (Case 1, 71% correct; Case 2, 71%; Case 3, 69%; $P < 0.05$ using χ^2 analysis for all subjects).

Subjects' explicit verbal responses were analysed as described previously. The rate of explicit stimulus identification, which ranged from 2 to 9% did not differ substantially from that noted on the previous categorization tasks; subjects did, however, tend to offer more incorrect explicit responses in this task. As noted in the previous categorization tests, most misidentifications appeared to be visually based ('John'→'Joan').

Word-to-picture matching

1. Across category

Evidence for word comprehension in the absence of explicit word recognition was also sought with a forced-choice task requiring the matching of a rapidly presented word to one of two pictures.

Methods. In the first test, the names of items pictured in the Boston Naming Test and Peabody Picture Vocabulary Test (Dunn, 1965) were used to create 31 pairs of words in both words shared at least the first 2 letters; this control was instituted to prevent subjects from using only information derived from a letter-by-letter analysis. Word pairs were matched for letter length (9 pairs, e.g., 'house'→'horse') or differed in length by one (8 pairs, e.g., 'whistle'→'whale') or 2 letters (14 pairs, e.g., 'propeller'→'pretzel'). The drawings appropriate to each pair of words were copied onto a single 11 × 8½ inch piece of white paper.

A randomized sequence of the 62 stimuli was presented briefly using the apparatus described above. Following the brief presentation, subjects were shown the sheet of paper on which the drawing appropriate to the stimulus and its matched word had been copied and asked to point to the appropriate picture. Each word was presented once; no feedback regarding response accuracy was provided. With two exceptions ('snake-snail' and 'broom-brush') pairs of words were drawn from different semantic categories.

Results. The data, expressed as percentage correct, are presented in Table 10. χ^2 analysis revealed that all subjects performed significantly above chance (1 df, $P < 0.25$). Eliminating from the analysis those rare trials in which subjects correctly identified a stimulus word did not appreciably alter the results. The frequency and accuracy of the subjects' explicit naming responses was similar to that reported in previous experiments.

2. Within-category

Methods. A within-category forced-choice word-to-drawing paradigm was performed in which subjects were asked to match animal names to pictures. Using stimuli from the Boston Naming

TABLE 10. WORD-TO-DRAWING MATCHING*

Case	*Different category (n = 62)*	*Within category (n = 30)*
1 (0.5 s)	87	90
2 (0.1 s)	69	—
3 (0.25 s)	74	87
4 (0.25 s)	66	73

* % correct.

Test and Peabody Picture Vocabulary Test, 14 pairs of animal names were generated. Because of the smaller number of possible stimuli, matching of the initial portion of the letter string was less rigorous than in the cross-category task above; thus, for 10 of the pairs the names shared only the first letter; 4 of the pairs contained the same initial 2 letter segment. Six of the pairs of animal names were matched for letter length, 2 pairs differed in length by 1 letter, 4 pairs differed by 2 letters and 2 pairs differed by 3 letters ('giraffe'→'goat' and 'beaver'→'butterfly'). A total of 23 different animal names was used; 7 names appeared twice, usually as part of a different pair of names (e.g., the stimulus 'snake' appeared twice, the first time paired on the answer sheet with the picture of a snail and the second with the picture of a spider). The testing procedure was identical to that described above. Subjects were told that a stimulus might appear more than once and were not given feedback regarding the accuracy of their responses during the session.

Results. Data for Cases 1, 3 and 4 are expressed in Table 10; data for Case 2 were not available. Once again, a χ^2 analysis revealed that all subjects performed significantly above chance (1 df, $P < 0.01$).

Discussion. Data from these studies suggest that all subjects were able to derive semantic information from words presented for brief intervals which they were rarely able to identify explicitly; the exclusion of those stimuli which the subjects could identify explicitly did not significantly alter the results.

An alternative explanation of these results is that the subjects adopted a conservative response bias, that they failed to offer an explicit response (i.e., name the word) because they were unsure and did not wish to be wrong. This would predict, however, that when subjects feel sufficiently secure to offer an explicit response, they should be correct. This was not observed; subjects were no more accurate in their explicit responses than with those stimuli they claimed not to have identified. We therefore believe that a conservative response bias is an unlikely explanation for these data.

It is of interest that Case 4, who performed at chance on a forced-choice object/nonobject task performed significantly better than chance on both the across-category and within-category tasks. One possible explanation for this is that she used orthographic information to access stored information about the visual features of the object and based her responses upon expectations regarding specific visual attributes. When presented with the word 'mouse', for example, she may have accessed information that the referent has a long tail and used this piece of information to distinguish between the drawings of a mouse and a moose. It should be noted that this hypothesis is consistent with her poor performance on the object/nonobject task; correct performance on that task required that the subject not only recognize components of an object but the relationships between the components.

Explicit word identification

Over the course of the weeks to months during which these subjects were studied, 3 of them (Cases 1-3) improved from an initial state characterized by an inability to 'see' more than single letters of briefly presented words to a point where they were able to explicitly identify a sizeable proportion of words presented for 0.25 s or less. Interestingly, Case 4, who was presumed to have suffered bihemispheric damage from systemic hypotension, was the only subject who failed to demonstrate substantial improvement in explicit word recognition.

The improvement in explicit word reading was associated with a clear change in the subjects' behaviour and explicitly verbalized strategy; by the time that subjects could identify rapidly presented words, they seldom named individual letters and denied using their previous strategy of letter-by-letter reading.

A series of investigations was performed in an attempt to elucidate the variables which may have influenced this explicit reading. Specifically, as we hypothesized that the reading of these subjects was mediated by right hemisphere mechanisms, we investigated the effects of part of speech and imagery, variables thought to influence the reading performance of the right hemisphere (Saffran *et al.*, 1980; Coltheart, 1983)

Experiment 1: part of speech

Methods. The possible effects of part of speech were assessed by asking subjects to read aloud a randomized list of 30 functors and 30 nouns matched for frequency (mean log frequency 2.67 ± 0.40 and 2.59 ± 0.27, respectively) and length (mean letter length 4.97 ± 1.11 and 5.01 ± 1.14, respectively). As described previously, words were presented with a microcomputer. The exposure times are indicated in Table 11.

TABLE 11. NOUN VS FUNCTOR—ORAL READING*

Case	*Nouns*	*Functors*
1 (0.25 s)	77	47
2 (0.1 s)	77	50
3 (0.25 s)	83	40

* % correct.

Results. The percentage of nouns and functors correctly read aloud by Cases 1–3 are shown in Table 11. Cases 1 and 3 identified significantly more nouns than functors ($\chi^2 = 5.71$, $\chi^2 = 10.33$, df = 1, respectively, both $P < 0.05$); although Case 2 also identified a greater proportion of nouns, the difference did not reach significance ($\chi^2 = 3.45$, df = 1, $0.10 > P > 0.05$).

Errors were classified as omissions, visually based word substitutions, 'unrelated' word substitutions in which no clear visual, semantic or phonological similarity between the stimulus and response was apparent, or 'partial letter information' errors in which only 1 or more letters from the stimulus were reported. For each subject, the percentage of each of these types of errors elicited by functors and nouns is expressed in Table 12; the absolute number of each error type as a function of stimulus class is expressed in parentheses. Although the small numbers make a formal analysis difficult, it would appear that the major difference in the errors for functors and nouns was the greater frequency of functor omissions. No semantic errors were noted.

TABLE 12. NOUN/FUNCTOR ORAL READING—ERROR ANALYSIS*

	Case					
	1		*2*		*3*	
Error type	*N*	*F*	*N*	*F*	*N*	*F*
Omission	14(1)	56(9)	17(1)	38(6)	40(2)	53(10)
Visual error	86(6)	38(6)	67(5)	54(8)	60(3)	47(8)
Unrelated	0	6(1)	17(1)	8(1)	0	0
Partial letter information	0	0	0	0	0	0

* % of errors.

TABLE 13. HIGH VS LOW IMAGERY WORDS—ORAL READING*

Case	*High*	*Low*
1 (0.25 s)	88	63
3 (0.25 s)	98	65

* % correct.

Finally, 2 normal controls (aged 58 and 67 yrs) were tested with the stimuli and apparatus described above. Exposure times were manipulated to produce error rates approximating those of Cases 1-3. With exposure times of 66 and 83 ms, both normal subjects exhibited error rates of approximately 35%; errors were equally divided between nouns and functors.

Experiment 2: word imagery

Methods. The effect of word imagery on oral reading was also assessed by asking subjects to read aloud a randomized list of 20 nouns of high imagery (> 5.0, Paivio *et al.*, 1968) and frequency (all > 60, mean frequency = 177.4±82.8; Kucera and Francis, 1967), 20 nouns of high imagery (> 5.0) and low frequency (all < 20, mean 6.5±4.3), 20 nouns of low imagery (< 3.0) and high frequency (all > 60, mean 178.6±121.8) and 20 nouns of low imagery (< 3.0) and low frequency (all < 20, mean 8.9±6.38). All groups of stimuli were matched for word length (mean of 5.6 letters for all groups). As before, stimuli were presented by a microcomputer with exposure times as indicated in Table 13.

Results. Cases 1 and 3 manifested a significant effect of word imagery; both subjects read aloud high imagery words significantly more accurately than low imagery words ($\chi^2 = 12.86$, df = 1, $P < 0.001$ and $\chi^2 = 13.87$, df = 1, $P < 0.001$, respectively). Collapsing across word imagery, Case 3 was significantly more accurate with high than low-frequency words ($\chi^2 = 6.65$, $P < 0.01$); Case 1 also performed better with high than low-frequency words but this effect was not significant. Unfortunately, data from Case 4 were not available.

Most incorrect responses were visual errors or omissions; 13 of the 14 omissions were noted with low imagery words.

Discussion. Thus all subjects with pure dyslexia who regained the ability to explicitly identify rapidly presented words performed better with nouns than functors and better with high than low imagery words. As previously pointed out by Allport and Funnell (1981), the part of speech effect may reduce to an imageability effect since functors are low in imageability; in any case, these data are consistent with the hypothesis that the reading of these subjects was mediated by the right hemisphere.

Processing of affixes

Experiment 1: oral reading of suffixed words

The distinction between 'open-class' and 'closed-class' words has been found to be a significant determinant of performance on a variety of language comprehension and production tasks in normal (e.g., Garrett, 1980) and brain-damaged (e.g., Friederici and Schoenle, 1980) subjects. In this context, the 'open-class' includes the major lexical items such as nouns, verbs and modifiers; the 'closed-class', in contrast, includes free-standing lexical items such as pronouns, conjunctions, articles, as well as bound morphemes (that is, affixes) which primarily serve grammatical functions.

The previous experiment, in which Cases 1-3 were asked to read aloud nouns and functors, demonstrated that the subjects were significantly more accurate in reading aloud open-class as compared to free-standing closed-class items. The following experiment was performed to determine if these subjects were also impaired in the oral reading of bound closed-class morphemes.

Methods. Forty pairs of words containing the same potential free-standing root morpheme (e.g., 'flow') were generated; 1 of the pair of words was suffixed (e.g., 'flowed'), while the other word was not suffixed but ended in a letter sequence which, in a different context, could be a suffix (e.g., '-er' as in 'flower'). For each word pair, the suffixed and pseudosuffixed words differed in length by no more than one letter. The mean frequency of the suffixed words was slightly higher (22.1 ± 39.1 vs 32.6 ± 43.9; Kucera and Francis, 1967), but this difference was not significant. These stimuli were presented in a random sequence; subjects were asked to read each word aloud. Stimuli were presented with a microcomputer using the exposure intervals indicated in Table 14.

Results. The percentage of words correctly read aloud by each subject is presented in Table 14. All subjects read aloud significantly more pseudosuffixed than suffixed words ($P < 0.001$ for all).

As the treatment of the suffixes and pseudosuffixes is of critical significance in

TABLE 14. SUFFIXED VS PSEUDOSUFFIXED WORDS—ORAL READING*

Case	*Suffixed*	*Pseudosuffixed*
1 (0.25 s)	30	73
2 (0.1 s)	50	88
3 (0.25 s)	33	83

* % correct.

TABLE 15. ORAL READING OF SUFFIXED VS PSEUDOSUFFIXED WORDS: ERROR ANALYSIS*

	Case					
	1		*2*		*3*	
	Suffix	*P-S*	*Suffix*	*P-S*	*Suffix*	*P-S*
Root						
Omission	1	2	0	0	4	3
Visual error	16	9	7	4	21	14
Suffix (P-S)						
Omission	20(7)	(1)	16(11)	(0)	35(12)	(1)
Substitution	3	(2)	1	(0)	2	(0)
Addition	0	(0)	0	(1)	1	(0)

* Number of errors; suffix omissions but correct reading of the root given in brackets.

the present context, each incorrect response was scored independently with respect to the root morpheme and suffix. Thus, for example, the response 'followed' to the stimulus 'flowed' was scored as correct with regard to the suffix but as a visual error involving the root ('flow'→'follow'); the response 'flower' to the stimulus 'flowed' was scored as a visual error involving the root morpheme and an omission of the suffix. Finally, for suffixed words, the failure to respond to a stimulus was scored as an omission of the root morpheme as well as an omission of the suffix. As each response was scored independently with respect to the root morpheme and suffix, the total number of errors noted in Table 15 may exceed the number of incorrect responses as reflected in the subject's raw score.

The number and breakdown of errors made by Cases 1-3 to suffixed ('Suffix') and pseudosuffixed ('P-S') words is expressed in Table 15. For suffixed and unsuffixed words, most errors which involved the root morpheme appeared to be visually based. For all 3 subjects, the most common errors were suffix omissions; in many cases, the root was correctly read but the suffix omitted (e.g., 'flowed'→'flow'); the number of errors of this type for each subject is indicated in parentheses next to the total number of suffix omissions in Table 15.

In contrast, the analogous error with pseudosuffixed words, the omission of pseudosuffixes to yield a legal free-standing root morpheme (e.g., 'flower'→'flow'), was rare; the precise number of such omissions is recorded in parentheses under the category of suffix omissions for pseudosuffixed words. Case 1 also made 2 errors to pseudosuffixed words which might be interpreted as 'suffix' substitutions ('wallet'→'walls', 'sparkle'→'sparked').

Although the frequency of the suffixed and pseudosuffixed words did not differ, the mean frequencies of the 'suffixes' included in the two groups of stimuli were significantly different (714±274 for the suffixed words, 319±295 for the pseudosuffixed words as measured by frequency counts for the 'suffixes' in the terminal position of 4-7 letter words; Mayzner and Tresselt, 1965; Mayzner *et* *al.*, 1965). To ensure that the observed difference in performance between pseudosuffixed and suffixed words was attributabe to morphological as opposed to orthographic factors, a separate analysis was performed for the 9 pseudosuffixed and 30 suffixed stimuli which ended in '-ed' or '-er'. Case 1 correctly read 9 of 9 pseudosuffixed words ending in '-er' and 14 of 30 suffixed words ending in '-er' or '-ed'. Cases 2 and 3 correctly read 8 and 9 pseudosuffixed words and 16 and 12 of the suffixed words, respectively. Using a χ^2 analysis, performace was significantly better with pseudosuffixed as compared with suffixed words matched for 'suffix' frequency ($P < 0.05$ for all subjects). These data suggest that the difference in performance with suffixed as compared with pseudosuffixed words is attributable to morphological rather than orthographic factors.

Thus when asked to read aloud suffixed and pseudosuffixed words matched for frequency and sharing the same potential root morpheme, subjects manifested a significantly greater impairment in reading aloud suffixed as compared with pseudosuffixed words. These data suggest that the impairment in reading these words reflects impaired processing of suffixes rather than simply a neglect of word endings.

Experiment 2: Lexical decision test with suffixed stimuli

Although the previous experiment demonstrated that Cases 1–3 were selectively impaired in the oral reading of suffixed words, the results do not indicate the functional locus of the impairment. Thus, for example, this impairment could reflect a failure in the production of affixed words or in earlier stages of processing. In an attempt to distinguish between these possibilities, a lexical decision test employing suffixed and unsuffixed words was performed. If our subjects were able to perform this task correctly, their difficulty in reading affixed words aloud would appear to lie in using visually presented affix information for production. Failure on the lexical decision task would imply some deficiency in dealing with affixes at earlier stages in the processing of graphemic information.

Methods. Cases 1 and 3 were given the test developed by Shallice and Saffran (1986). Stimuli for this test included 63 root morphemes between 5 and 9 letters in length. The root morphemes included an equal number of nouns, adjectives and verbs. Each root morpheme was presented on three occasions: in an unaffixed form (e.g., 'elephant'), appropriately suffixed (e.g., 'elephants'), and inappropriately suffixed (e.g., 'elephanting'). For nouns, the appropriate suffix employed was -s, for adjectives appropriate suffixes included -ly, -(i)er, and -(i)est, and for verbs appropriate suffixes included -s, -ed, and -ing. The same suffixes were used to generate inappropriately suffixed words.

Stimuli also included 63 nonwords generated by changing 2 letters in each of the 63 root morphemes; each nonword appeared twice, once unsuffixed and once in conjunction with the suffix appropriate to the word from which it was derived.

The test was administered in three sessions; in each session, 7 blocks of 15 stimuli were presented; each block contained 1 unsuffixed, 1 appropriately suffixed and 1 inappropriately suffixed form of a noun, adjective and verb as well as 3 suffixed and 3 unsuffixed nonwords. Each root morpheme appeared once in each session.

As 2 subjects performed at chance with every category of stimuli on the test described above, a

TABLE 16. SUFFIXED WORD LEXICAL DECISION TEST*

	Words			*Nonwords*	
Case	*Unsuffixed*	*Correct suffix*	*Incorrect suffix*	*Suffixed*	*Unsuffixed*
1 (n = 62) (0.25 s)	63	63	65	19	37
2 (n = 40) (0.1 s)	88	78	75	13	13
3 (n = 62) (0.25 s)	84	79	73	40	32
4 (n = 40) (0.25 s)	85	75	65	18	18

* % 'yes' responses

second version of this test was constructed which was similar in most respects but utilized higher frequency root morphemes.

Stimuli for this study included 40 unsuffixed words (20 nouns, 20 verbs), 40 appropriately suffixed words, 40 root morphemes with inappropriate suffixes (e.g., 'wifed'), 20 unsuffixed nonwords and 20 suffixed nonwords. All root morphemes were greater than 100 counts per million in frequency (Kucera and Francis, 1967) and varied in length between 3 and 6 letters. The same suffixes were used for the appropriately and inappropriately suffixed root morphemes as well as for the suffixed nonwords. Nonwords were derived from high frequency (> 100; Kucera and Francis, 1967) root morphemes by changing a single letter. The test was administered in two sessions.

For all subjects, stimuli were presented with a microcomputer for brief intervals as indicated in Table 16. Subjects were told to indicate if the stimulus was a real word or not; subjects were informed that some 'real' words would have incorrect endings and that these words were to be considered as nonwords. As before, subjects were instructed to attempt to derive a 'feeling' for or 'intuition' about the stimulus rather than to attempt to explicitly identify the stimulus and to notify the experimenter if they believed that they had identified a word.

Results. The data, expressed as the number of 'yes' responses, for all subjects are presented in Table 16. All subjects successfully discriminated between unsuffixed words and nonwords. The critical comparison in this context, however, is between the performance on appropriately and inappropriately suffixed words. No subject reliably distinguished between appropriately and inappropriately suffixed words.

Discussion. These results demonstrate that all our subjects were impaired in the processing of suffixes; more specifically, the finding that the impairment is observed even when oral reading is not required indicates that the limitation must involve processes that occur prior to the programming of verbal output. These results parallel those of Shallice and Saffran (1986) in their study of an alexic patient.

In a broader context, there are several possible interpretations for these results. If, as was hypothesized previously, the patients' reading is mediated by right hemisphere mechanisms, these data suggest that neither affixed words nor a system for determining the legality of roots and affixes is represented in the right hemisphere. In conjunction with the results of the previous oral reading tasks demonstrating an impairment in the reading of functors, these data suggest that the right hemisphere is deficient in the processing of all aspects of closed-class morphology.

Finally, these data are not predicted by the disconnection account of pure alexia in which the impairment is assumed to be attributable to a failure of input to reach preserved left hemisphere processing mechanisms. Even if an attempt is made to explain the relatively good performance of our subjects on lexical decision tests with unaffixed words by hypothesizing that the disconnection is only 'partial', this theory does not explain why suffixes should be more 'disconnected' than word roots.

GENERAL DISCUSSION

Reading and the right hemisphere

Although in 'classical' accounts, the right hemisphere was considered to be 'word-blind', in recent years evidence has been adduced suggesting that the right hemisphere in normal right-handed subjects may have the capacity to read. On the basis of studies with normal subjects, evaluations of patients after sectioning the corpus callosum, investigations of patients after left hemispherectomy and studies of patients with acquired language disturbances such as deep dyslexia, Coltheart (1980, 1983), for example, has suggested that the right hemisphere supports a lexicon which can be accessed by orthographic input. Additional data supporting this contention is provided by a report of a patient who recovered from alexia due to a left hemisphere vascular lesion but subsequently became profoundly and permanently alexic after a second right hemisphere vascular lesion (Heilman *et al.*, 1979).

The putative right hemisphere language capacities are thought to differ in a number of important respects from those of the left hemisphere. Because split-brain patients are generally unable to perform rhyme judgements on words presented to the right hemisphere, or read aloud words presented to the right hemisphere which they can match to an object, it is often assumed that the right hemisphere does not support speech output mechanisms or the ability to derive phonology from print (Saffran *et al.*, 1980; Zaidel and Peters, 1981; Coltheart, 1983). Investigations of reading in split-brain patients have suggested that the putative right hemisphere lexicon consists primarily of concrete or high imagery open-class nouns; some, but by no means all, studies of normal subjects have also suggested that the right hemisphere lexicon includes primarily concrete nouns (*see* Patterson and Besner, 1984, for a review of this controversial topic). Additionally, investigations of deep dyslexics and split-brain patients has led Coltheart (1980, 1983) to postulate that semantic errors (e.g., 'uncle'→'cousin') are characteristic of right hemisphere reading. Finally, it has been claimed that the right hemisphere reading mechanisms permit greater success with logographic (e.g., Kana) as compared with syllabic scripts (e.g., Kanji) (Sasanuma, 1980).

Data from our patients are in accord with the right hemisphere reading hypothesis in several important respects. In the following sections dealing with tacit reading, explicit reading and the processing of affixes, the implications of our patients' data for this and competing accounts of pure alexia will be discussed.

Tacit processing

All subjects discriminated words from nonwords and performed better than chance on a variety of semantic categorization tasks with rapidly presented stimuli which they were unable to identify explicitly. Thus these subjects demonstrated the phenomenon of reading without awareness or 'tacit' reading.

Similar phenomena have been demonstrated in normals (Marcel, 1983*a*). To account for this finding in normal subjects, Marcel (1983*b*) proposed that the processing of sensory information is distinct and dissociable from awareness or consciousness. Thus subjects may use the normal processing mechanisms to derive semantic information from rapidly presented visual verbal stimuli but be unaware of this processing because the stimuli do not engage those additional mechanisms which provide the subjective sensation of awareness. One possible account of the tacit reading of subjects with pure alexia (Shallice and Saffran, 1986), for example, suggests that these subjects employ the left hemisphere-based visual word form system normally used to process visually presented words but that this system is partially disrupted, preventing a link to those processes mediating consciousness.

An alternative account is that tacit processing may depend on processing mechanisms which are functionally and anatomically distinct from those normally employed in explicit word recognition. As pointed out by Shallice and Saffran (1986), this is the type of explanation offered for the phenomenon of 'blind-sight' in which hemianopic patients have been shown to process visual input directed to the 'blind' field (Weiskrantz *et al.*, 1974). Such an account may also be proposed to explain tacit reading in pure alexia. As primary visual information is restricted to the right hemisphere in most subjects with pure alexia, one obvious candidate for the locus of tacit reading mechanism in this syndrome is the right hemisphere. It is noteworthy that the explicit denial of the ability to 'see' more than single letters despite evidence of preserved lexical access is reminiscent of phenomena manifested by patients after surgical transection or lesions of the corpus callosum in which it is often assumed that the right hemisphere is processing information and generating motor responses without communication of these activities to the left hemisphere.

Explicit reading

Three of our 4 subjects regained the ability to identify rapidly presented stimuli explicitly. This recovery provided an opportunity to test other predictions of the right hemisphere reading hypothesis. As noted above, data from deep dyslexics and normals have led to the hypothesis that the right hemisphere lexicon consists primarily of open-class words of high imagery. Thus, if the reading of our subjects is mediated by the right hemisphere, better performance might be expected with nouns than functors and high as compared to low imagery words.

These predictions were, in fact, borne out. Cases 1 and 3 read nouns significantly better than functors; for Case 2 this effect did not quite reach significance. Cases 1 and 3 read high imagery nouns significantly more accurately than low imagery nouns.

There is one respect, however, in which the performance of these 3 subjects on oral reading tasks differs from that predicted by at least one version of the right hemisphere reading hypothesis (Coltheart, 1983): subjects made relatively few semantic errors. Although subjects not infrequently provided some semantic information pertinent to a stimulus which could not be explicitly identified and did exhibit within-category word substitutions on word categorization tests (e.g., 'tiger'→'lion'), semantic paralexias in which subjects were not biased by the experimental context were rare. The explanation for this finding is not clear. One possibility is that the subjects' responses were constrained by convergent input from both the right hemisphere-based semantic system and the (left hemisphere) visual word form system. As these subjects typically were able to identify explicitly at least the initial letter, it might be speculated that this information was available to the (left hemisphere) visual word-form system; thus, even if it is assumed that the right hemisphere-based semantic system does not permit complete specification of the stimulus at the level of the output phonological lexicon, partial information from the visual word form system might constrain the response generated at the phonological lexicon and reduce or eliminate semantic errors.

Alternatively, it could be speculated that, as semantic paralexic errors are typically encountered in subjects with extensive left hemisphere injury, the production of these errors requires both lack of precise specification of the appropriate semantic or output phonological lexical entry and a 'disinhibition' or willingness to respond in the absence of full specification of the appropriate entry; alternatively expressed, it is possible that the extensive left hemisphere injury lowers the response threshold, thereby creating a situation in which subjects are more likely to respond, and therefore, assuming incomplete specification of the target utterance, more likely to produce semantic paralexic errors.

On this line of reasoning, given a 'normal' response threshold, it might be predicted that subjects will not produce semantic errors but will fail to respond; interestingly, in all explicit word identification tasks, omissions, particularly to functors and low imagery words, were the second most frequent type of error.

It is noteworthy that the only subject (Case 4) who failed to regain the ability to identify words explicitly was also the only subject with clinical evidence of bihemispheric impairments. Although she did manifest a well defined infarct on CT scan, it should be noted that this infarct developed in the context of a hypotensive episode suffered during a coronary artery bypass operation; additionally, she failed to recognize family members by sight but could name them from their voices during the first postoperative week and thereafter manifested a visual object recognition impairment (that is, 'apperceptive visual agnosia') of moderate severity. As both prosopagnosia (which she may have initially manifested) and apperceptive visual agnosia are typically associated with bilateral posterior damage (Bauer and Rubens, 1985), it may be that she suffered ischaemic injury to the right hemisphere due to systemic arterial hypotension, a condition which may not be associated with well defined lesions on CT scan. It might be speculated, therefore, that she could perform above chance on lexical decision tests and semantic categorization tests by accessing a right hemisphere-based lexicon and semantic system but that the presumed ischaemic injury of the right hemisphere prevented sufficient specification of the lexical or semantic entry to permit explicit word identification.

Finally, there are a number of possible explanations for the improvement in explicit word reading in our subjects; our data do not appear to help adjudicate between them. One possibility is that the subjects regained access to the phonological lexicon of the left hemisphere, presumably by means of information transfer across the undamaged body of the corpus callosum; in this event, of course, the subjects' oral reading would not be exclusively dependent upon the right hemisphere but would presumably reflect the right hemisphere lexical-semantic capacities. Another possibility is that the right hemisphere developed the capacity to produce speech; this seems unlikely, however, since corpus callosotomy subjects typically do not develop the capacity to read aloud words presented to the right hemisphere.

Processing of affixes

Previous accounts of the language capacity of the right hemisphere have emphasized its lexical and semantic capabilities (Zaidel, 1978; Coltheart, 1983); in particular, these accounts have stressed the ability to derive meaning from print. Implicit in these accounts is the assumption that the right hemisphere does not support the capacity to decode or generate complex linguistic structures. As functors and bound morphemes, which together comprise the closed-class lexicon, convey relatively little semantic information but are critical for capacities assumed not to be supported by the right hemisphere (that is, syntax comprehension and production), it might be predicted that the closed-class lexicon would not be represented in the right hemisphere. As demonstrated by impaired oral reading of functors as compared to nouns, insensitivity to the appropriateness of suffixes and impaired oral reading of pseudosuffixed versus suffixed words, our subjects showed a significant impairment in the processing of all types of closed-class morphology. These data are consistent with the hypothesis that the reading of our subjects was mediated by right hemisphere mechanisms.

Alternative accounts of pure alexia

Although the previous discussion has emphasized the possible role of the right hemisphere in the residual reading performance of these subjects with pure alexia, there are a number of other accounts of this syndrome which must be considered.

Warrington and Shallice (1980), for example, argued that pure alexia is not attributable to an impairment of visual input to the left hemisphere but to a disruption of the visual word form system, a left hemisphere-based mechanism which serves to process visual verbal information and provide for word identification. As recently suggested by Shallice and Saffran (1986), this account can be extended to accommodate the findings of our subjects. For example, an impairment but not obliteration of the word form system may be associated with some activation of the appropriate entries but this activation may be insufficient for explicit identification; similarly, according to Shallice and Saffran (1986), the weak output of the damaged word form system may be sufficient to activate appropriate semantic entries but not sufficient to inhibit semantic associates and thereby permit precise semantic specification.

This hypothesis, however, is subject to at least two objections. First, it fails to account for the specific pattern of impairments demonstrated by our subjects on tests of explicit word identification. As the distinction between nouns and functors and high and low imagery words has not typically been assumed to be relevant to the visual word form system, it is not clear how the significant effects of imagery and part of speech manifested by our subjects would be associated with damage to this system. The second point concerns the anatomical substrate of the putative visual word form system; although not explicitly stated by Warrington and Shallice (1980), it might be assumed this system is critically dependent on the cortex of the posterior portion of the left hemisphere. At least one of our patients (Case 1), however, had no evidence of damage extending into or undercutting the cortex; thus damage to a cortically represented processing mechanism such as the visual word form system cannot readily account for at least some cases of pure alexia.

Patterson and Kay (1982) proposed that pure alexia is caused by a pathological limitation in the ability to transmit letter information in parallel; they proposed that multiletter segments and words cannot be accommodated by the compromised system but that single letters can be identified and successfully transmitted. On their analysis, the phenomenon of letter-by-letter reading which is often observed in subjects with pure alexia, reflects the operation of the visual word system (or visual input logogen) with sequential as opposed to parallel letter information.

With some modification, this proposal can account for our data; thus, for example, it might be proposed that parallel transmission of letter information is in fact achieved, but that this input to the word form system is 'weak' and does not support full activation of the appropriate entry. The problem with this hypothesis is that aberrant input (that is, serial access) to the visual word form system leads to more adequate output, permitting explicit identification of the word, than normal (that is, parallel) input. As Shallice and Saffran (1986) point out, this seems unlikely. This hypothesis is also subject to the same objection noted above: it provides no principled account of the imagery and word class effects demonstrated by our subjects.

Strategy differences

We have argued that the performance of the our subjects is consistent with the hypothesis that the right hemisphere is literate. A proposal that this is a general account of the syndrome, however, must accommodate the observation that most patients with pure alexia have *not* been demonstrated to exhibit the reading capacities demonstrated by our subjects; indeed, the apparent absence of reading ability in patients with pure alexia has been cited as compelling evidence against the right hemisphere reading hypothesis (Patterson and Besner, 1984). There are several important points in this regard.

First, although the vast majority of patients with pure alexia have not shown any ability to process print except by a letter-by-letter strategy, there have been a number of patients with pure alexia who have demonstrated at least some of the phenomena reported here. Landis *et al.* (1980), for example, described a right-handed patient who developed pure alexia secondary to a left posterior glioblastoma multiforme; on 5 of 7 trials, this patient was able to point to the object corresponding to a briefly presented word which he was unable to identify explicitly. Grossi *et al.* (1984) reported a patient with pure alexia following a left occipital infarct who could explicitly identify letters (38/42 correct) but could not identify words (2/50 correct) even with prolonged exposure; in the absence of explicit identification, however, this subject could match pictures, objects and auditory words to 1 of 10 written words correctly (9/12, 9/12, 10/12 respectively). Finally, Shallice and Saffran (1986) reported a patient with pure alexia and letter-by-letter reading who performed above chance on lexical decision tests and at least some tests of semantic categorization with stimuli presented for too brief an interval to permit explicit identification.

Thus there is evidence that at least some subjects with pure alexia can access lexical and even semantic representations for words which they are unable to identify explicitly. In addition, as forced-choice tests of lexical decision and semantic categorization in the absence of explicit identification have not been reported for most patients with pure alexia, it might be argued that the heavy emphasis on oral reading has resulted in a consistent underestimation of the true capacities of these patients.

This explanation alone, however, cannot explain the discrepancy between our subjects and some of the other patients reported in the literature. There are at least two reports of subjects with pure alexia in which seemingly appropriate paradigms were employed but no evidence of implicit reading was found (Warrington and Shallice, 1980; Patterson and Kay, 1982). A number of possible explanations for the discrepancy should be considered. One is that normal subjects vary in the degree to which language is represented in the right hemisphere. Although this hypothesis is subject to the serious criticism that it is consistent with almost any pattern of performance and therefore not testable, this fact alone does not invalidate the hypothesis; Shallice and Saffran (1986) have discussed a number of points which lend credence to the notion that there is variation among normals in the degree to which language is represented in the right hemisphere.

Another possible explanation for the difference between the performance of our subjects and most subjects with pure alexia is that different strategies may have been employed by different subjects. Our subjects were encouraged not to attempt to explicitly identify words using a letter-by-letter approach but were, rather, urged to develop a 'feeling for' or 'intuition' about the entire letter string. Although definitive evidence of strategy use is not available, it was our strong impression that when subjects attempted to use a letter-by-letter strategy, as they all did initially, there was no convincing evidence of better than chance performance on lexical decision and categorization tasks. With continued exhortations not to use a letter-by-letter strategy, however, our subjects appeared gradually to make a transition to a reading strategy in which the focus was the attempt to achieve what one subject described as a 'sense for the word'. Concomitant with this shift in strategy was an apparent reduction in the explicit use of a letter-by-letter strategy (i.e., subjects reported initial letter information less frequently) and an improvement in performance on lexical decision and categorization tests.

Thus we suggest that our subjects could process visual verbal information in two quite different manners: subjects could identify individual letters and, perhaps using the left hemisphere-based spelling mechanism in a reverse fashion (Warrington and Shallice, 1980; Shallice and Saffran, 1986), use sequential letter information to identify words; additionally, subjects appeared to use a 'whole word' (or more precisely, a root morpheme) mechanism to access a right hemisphere-based lexicon. Perhaps because of an association between left hemisphere-based language mechanisms and conscious awareness of language processing, subjects were explicitly aware of the output of letter analysis mechanism but were not, at least initially, explicitly aware of the output of the right hemisphere-based analysis. We suggest that because of the repeated recommendations of the investigators and the disconcerting but ultimately overwhelming evidence that they performed better when they attempted to derive a 'feeling' for the stimulus, subjects increasingly acted upon the output of the right hemisphere based mechanisms.

Strategy differences were also invoked by Landis *et al.* (1980) and Shallice and Saffran (1986) to account for their data. Landis *et al.*, for example, suggested that initially their patient used visually-presented words to access a right hemisphere-based semantic store; the subsequent use of a letter-by-letter strategy with a goal of explicit word identification, they argued, inhibited or disrupted this right hemisphere-based process. Similarly, Shallice and Saffran (1986) argued that M.L. used a letter-by-letter strategy in tasks requiring word recognition but employed a different strategy when rapid stimulus presentation prevented explicit word identification.

Finally, the hypothesis that strategy differences critically affect performance offers a possible explanation for the apparent lack of implicit word processing demonstrated in the careful investigations by Warrington and Shallice (1980) and

Patterson and Kay (1982). Although in both these investigations, subjects were given forced-choice tests similar to those employed with our subjects, the emphasis appears to have been placed on explicit word identification rather than implicit processing; that is, as they wished to determine if subjects could derive information about words which had not been explicitly identified, they asked subjects to first name the word; only if they failed were they asked to make a judgement about the word (e.g., word vs nonword). In other tasks, Patterson and Kay's (1982) subjects were asked to make judgements before attempting to name words; however, in these tasks stimuli were presented across a desk and it is, therefore, not clear that subjects' standard letter-by-letter strategy was untenable. We would argue that the emphasis on explicit naming in most of these tasks reinforced the subjects' use of the letter-by-letter strategy and discouraged the use of alternative strategies; once again it should be noted that our subjects were constantly urged *not* to attempt to identify words explicitly and their performance appeared to be inversely correlated with the commitment to a strategy of explicit word identification. Thus we would propose that the apparent inconsistency between our data and those of Patterson and Kay (1982) and Warrington and Shallice (1980) is attributable to a subtle but critical difference in methodology which had the effect of encouraging different processing strategies in the different studies.

Therapy

If our account of the influence of strategy differences is correct, the letter-by-letter reading strategy, which is commonly advocated for the treatment of pure alexia, may be counterproductive. Although this strategy may be useful in some subjects, it typically permits only slow and effortful reading. We contend that it would be more appropriate to attempt to encourage subjects to change strategy and access the right hemisphere mechanisms. In this context, it is of note that although subjects with pure alexia usually do not show substantial improvement (Ajax, 1967; Benson and Geschwind, 1976), all 3 of our subjects with unilateral left hemisphere damage improved considerably. However, as all our subjects were tested within several months of the onset of symptoms, this improvement cannot unequivocally be attributed to the strategy change discussed above.

Rothi *et al.* (1985), however, have reported a subject with a 4 yr history of pure alexia and letter-by-letter reading subsequent to a left occipital infarct who demonstrated substantial improvement following a course of therapy designed specifically to encourage the use of a 'gestalt' reading strategy. In a month-long course of remediation involving a variety of tasks in which stimuli were presented tachistoscopically, these investigators demonstrated significant improvement on tests of semantic categorization and lexical decision and improvement of one grade on the Spache Diagnostic Reading Scales (1963).

The case of Rothi *et al.* (1985) is also of note because it provides indirect support for the thesis that the improvement noted by our subjects is attributable to a shift in *strategy* rather than a change in the physiological capacity of specific brain structures such as the corpus callosum; thus, while the gradual improvement in our subjects might be attributed to gradually resolving ischaemic dysfunction of the corpus callosum or the left occipital pathways implicated in reading, such an explanation would not account for improvement noted 4 yrs after brain infarction.

Finally, these data demonstrating at least relatively preserved tacit processing without subjective awareness attest to the utility of forced-choice and other indirect measures of performance in the assessment of subjects with brain injury. In conjunction with previous investigations of amnesic (e.g., Schacter and Graf, 1986) and prosopagnosic (e.g., Bauer and Rubens, 1985) subjects demonstrating preserved processing without awareness, these data reinforce the notion that a comprehensive understanding of cognitive function must address not only information processing mechanisms but the elusive phenomena of consciousness with these mechanisms are so complexly articulated.

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COGNITIVE IMPAIRMENT IN PATIENTS WITH CLINICALLY ISOLATED LESIONS OF THE TYPE SEEN IN MULTIPLE SCLEROSIS

A PSYCHOMETRIC AND MRI STUDY

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SUMMARY

This study reports the performance on psychometric tests of a group of 48 patients with clinically isolated lesions of the type seen in multiple sclerosis (optic neuritis, brainstem and cord lesions). The cognitive functions studied were: 'IQ deficit', verbal and visual memory, abstracting ability, visual and auditory attention, and naming ability. The presence of brain pathology was investigated by means of magnetic resonance imaging (MRI). A group of 46 patients with rheumatic and neurological conditions not known to cause brain disease was used for comparison. Normative MRI data were obtained from a group of 40 normal volunteers.

An overall 'Cognitive Ability Index' was significantly worse in patients with clinically isolated lesions when compared with physically disabled controls. IQ deficit and defective auditory attention were the more severely affected parameters. These deficits were significantly correlated with the duration of neurological symptoms and with the degree of brain pathology detected by MRI.

INTRODUCTION

Cognitive decline in patients suffering from multiple sclerosis (MS) was first mentioned in reports published over a hundred years ago (Charcot, 1877). Cases of rapidly progressive dementia attributed to the presence of widespread lesions in the white matter have also been reported (Bergin, 1957). However, the systematic study of the cognitive abnormalities which might be present in a large number of patients with definite MS has only been attempted recently.

Deterioration in nonverbal skills (Reitan *et al.*, 1971; Ivnik, 1978), memory (Beatty and Gange, 1977; Grant *et al.*, 1984; Rao *et al.*, 1984), and abstracting ability (Parsons *et al.*, 1957) have now been documented in patients with definite MS, sometimes occurring during the early stages of the disease. Attempts have also been made to correlate these deficits with the presence of brain pathology as detected by computerized tomography (Rao *et al.*, 1985; Rabins *et al.*, 1986), or

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with nonspecific functional abnormalities such as decreased blood flow as measured by positron emission tomography (Brooks *et al.*, 1984).

Magnetic resonance imaging (MRI) has made it possible to detect MS lesions with much greater sensitivity than previous techniques (Young *et al.*, 1981), enabling us to make more accurate clinicopathological correlations. It has also made possible the study of brain pathology in patients with clinically isolated lesions of the type known to occur in MS, namely optic neuritis, brainstem and cord lesions. Ormerod *et al.* (1987), using MRI, have found lesions in brain areas other than those responsible for the presenting symptoms in over half of these patients at the time of the initial presentation. Optic neuritis, the best studied of these clinically single lesions, is the first manifestation of MS in about 20% of cases and approximately three-quarters of those with this initial presentation go on to develop definite MS (Francis *et al.*, 1987). Prospective follow-up studies have not been performed in those with brainstem or cord lesions, but it appears likely that a similar proportion ultimately develops MS (McDonald and Silberberg, 1986).

The cognitive performance of patients with clinically isolated lesions has only been studied in a handful of cases (Lyon-Caen *et al.*, 1986) and the possibility that subtle psychometric abnormalities may be one of the earliest counterparts of brain pathology remains to be explored. Clinically isolated lesions provide a unique opportunity to study cognitive abnormalities before the severe physical limitations of the disease become apparent, thus avoiding some of the methodological problems that make interpretation of test results difficult in those with definite MS (Rao, 1986).

We report here a study of the psychometric performance of a group of patients with clinically isolated lesions in whom the presence of brain pathology in areas other than those responsible for the symptoms was examined using MRI. The test battery used in the study was chosen to assess those abilities known to be impaired in patients with definite MS. In addition, tests of attention, a function likely to be impaired in patients with deep white matter lesions, were also used.

METHODS

Subjects

Patients with clinically isolated lesions. Forty-eight right-handed patients (18 men and 30 women) with clinically isolated lesions were included in the study; 14 presented with optic neuritis, 16 with brainstem syndromes and 18 with symptoms from a spinal cord lesion. The patients were part of a large cohort undergoing a study of MRI abnormalities in MS at the National Hospital for Nervous Diseases. Their ages ranged from 20 to 61 yrs, with a mean of 36.4 yrs. The diagnosis of a clinically isolated lesion of the type commonly found in MS was made after they had undergone appropriate neurological assessment to exclude other possible aetiologies. Special attention was given to the duration of the neurological symptoms and to whether the patients were in exacerbation at the time of testing. Exacerbation was defined using the Poser *et al.* (1983) criteria as a symptom or symptoms of neurological disturbance, with or without objective confirmation, lasting more than 24 h.

Forty-three patients were physically independent, 2 required walking aids and 3 were wheelchair bound. Seven patients were receiving corticosteroids and 14 were taking benzodiazepines (mainly as night sedation) at the time of the study. Subjects were excluded if they had sustained head injuries with a posttraumatic amnesia of more than 24 h, or if there was evidence of drug or alcohol abuse. Only those whose first language was English and who had received their primary education in the UK were included in the study.

Seventeen patients were in relapse at the time of testing. Corrected visual acuity was normal in all, except for 7 with unilateral optic neuritis who were in relapse. Tests of visual attention were not performed by these 7 patients.

Control subjects. Two groups of control subjects were assessed for comparison. A physically disabled control group consisted of 46 patients (18 men and 28 women) suffering from neurological or rheumatic conditions not involving the central nervous system. Twenty-two patients had prolapsed intervertebral discs, 7 had peripheral neuropathy, 5 muscular dystrophy, 2 spinal cord tumours, 9 rheumatoid arthritis and 1 plantar fasciitis. Their ages ranged from 20 to 68 yrs, with a mean of 39 yrs. All had normal (corrected) visual acuity and 2 were left handed. Two of them were receiving corticosteroids, 27 were on benzodiazepines (mainly as night sedation), and 3 were on antidepressants at the time of the study.

Subjects in the physically disabled control group were more disabled than those with clinically isolated lesions. Thus only 27 were physically independent, 9 required walking aids and 10 used wheelchairs.

A second control group of 40 normal volunteers (21 men and 19 women) were used to obtain normative MRI data. The subjects in this group were officers in the Salvation Army who volunteered to take part in the study. Their ages ranged from 19 to 64 yrs, mean 39.9 yrs. The exclusion criteria used for the clinically isolated lesion group were applied to the control subjects.

Psychometric assessment

The following tests were administered to the patients with clinically isolated lesions and to the physically disabled controls.

1. National Adult Reading Test (NART) and Schonell Graded Word Reading Test. These tests were administered following the standard procedure of Nelson (1982) to provide an estimate of premorbid intelligence and their combined scores were transformed to IQ equivalents.

2. Weschler Adult Intelligence Scale (WAIS). A shortened version was used (Weschler, 1955) and the following subtests administered: Arithmetic, Similarities, Digit Span, Vocabulary (verbal subtests), Picture Completion, Picture Arrangement and Block Design (performance tests). The results were prorated to yield measures of Verbal, Performance and Full Scale IQ. The difference between the estimated premorbid IQ and the full scale WAIS IQ was considered as an index of deterioration, hereafter referred to as IQ deficit.

3. Recognition Memory for Words (Warrington, 1984). This was administered following the standard procedure. The test consists of 50 stimulus words. Recognition memory was tested by presenting each of the words paired with a distractor, the subject being required to make a forced choice between them. The raw score (number of words correctly recognized) was converted to an age-corrected scaled score.

4. Recognition Memory for Faces (Warrington, 1984). Fifty black and white photographs of unfamiliar male faces were the stimuli and the subject was asked to recognize them when each was paired with a distractor photograph drawn from a similar pool. The raw score (number of faces correctly recognized) was converted to an age-corrected scaled score.

5. Wisconsin Card Sorting Test. The shortened version of this test was used (Nelson, 1976). It consists of 1 set of stimulus cards and 2 sets of 24 response cards, the subject being asked to sort them according to 1 of 3 attributes in turn (colour, shape or number). The total number of errors was recorded as a measure of abstracting ability.

6. Speed of Letter Counting. This test is based on a letter cancellation task described by Willison *et al.* (1980) and consists of 90 large letters (19 As, Bs and Cs and 17 Ds and Es) arranged randomly

in 12 rows and 5 columns. The time taken to count the number of As on the page was recorded as a measure of visual attention.

7. Auditory Attention was tested using an adaptation of a vigilance task provided by E. Kaplan (personal communication, 1984). Five groups of 20 letters each were read at a speed of 1 letter per second and recorded on tape. Embedded among them was the alphabet in the conventional order. The subject was required to make a sign when he heard the first letter of the alphabet, then when he heard the second, etc., until the letter Z had been signalled. Before testing, the subjects were asked to recite the alphabet to ensure that they were familiar with it and they were given a practice run of 20 letters in which the first 5 letters of the alphabet were embedded. The test was interrupted if the subjects signalled at the wrong letter (false positive errors) or if the correct one was missed (false negative errors) in which case they were told the next letter they should be listening for. The total number of errors, positive and negative, was recorded as a measure of auditory attention.

8. Graded Naming Test. This object naming test of graded difficulty (McKenna and Warrington, 1983), consisting of 30 black and white line drawings, was administered following standardized procedures. The number of objects correctly named was recorded as a measure of naming skill.

The psychometric assessment lasted approximately 1 h 30 min. The tests were administered in the following order: naming, reading and memory tests, WAIS, tests of abstracting ability and attention tests. Thus 7 psychometric functions were examined: IQ deficit, Verbal Memory, Abstracting Ability, Visual Attention, Auditory Attention and Naming Ability. A grading system (0-3) was devised for each of these functions. Grade 0 was assigned to score at or above the 50th percentile of the control group, Grade 1 to scores falling within the 25th and 50th percentiles of the control group, Grade 2 to scores within the 5th and 25th percentiles, and Grade 3 to scores equal to worse than the 5th percentile of the control group. These grades were summed to provide an overall Cognitive Ability Index. A similar grading system (0-3) based on the distribution of the Cognitive Ability Index scores in the control group was applied to the overall Cognitive Ability Index scores in the isolated lesion group. Thus a Cognitive Ability Grade 0 represented the summed grades at or above the 50th percentile of the control group, Grade 1 the summed grades between the 25th and 50th percentiles of the control group, etc. This procedure makes the assumption that the various tests measure cognitive functions which are to some extent independent, and permits the combination of scores from different tests in which the units of measurement are not the same.

Motor assessment

A measure of hand function and a measure of the ability to perform everyday tasks were used in the patients with clinically isolated lesions and the physically disabled controls.

1. Jebsen Hand Function Test. This test (Jebsen *et al.*, 1969) comprises 8 standardized timed tasks of hand function. Seven of them (writing, maze tracing, card turning, simulated feeding, putting small objects into a can, picking up large light objects, and picking up large heavy objects) were performed with each hand in turn. The eighth task, assembling nuts and bolts, required the use of both hands. The final score was the sum of the times taken to accomplish the 8 tasks.

2. Activities of Daily Living. Seven standardized motor tasks related to everyday activities were tested: dressing, walking, climbing stairs, bathing, transfering from bed to chair, tea making and feeding. The scoring system was a modification of that used by Haworth and Hollings (1979). The patient's performance on each of these tasks was graded on a 4 point scale (0 = no assistance needed, 1 = help from others or mechanical aid required, 2 = help from others and mechanical aid required, 3 = unable to attempt or finish task). The final score was the sum of the partial scores.

Psychiatric assessment

Patients with clinically isolated lesions and the physically disabled controls were assessed psychiatrically. The methodology and results of this assessment have been reported elsewhere (Logsdail *et al.*, 1988). The Clinical Interview Schedule (CIS) (Goldberg *et al.*, 1970) was used for this purpose. The total score (range 0-33), which includes ratings of subjective symptoms and objective behaviour, was used in the analysis. Patients who scored 14 or more were considered to be psychiatric 'cases'.

MRI assessment

The imager used in the study was a 0.5 tesla Picker superconducting system used to form proton NMR images. The detailed methodology of the scan assessment has been reported elsewhere (Ormerod *et al.*, 1987). Briefly, the presence and size of lesions were examined in 7 periventricular areas (body of the ventricles, frontal, temporal and occipital horns, trigone, and third and fourth ventricles) and in the following areas of the brain parenchyma: internal capsule, basal ganglia, frontal, parietal, temporal and occipital lobes.

Lesions in each of these areas were scored from 0–3 depending on the size of their longest diameter (0 = 2 mm, 1 = 2–5 mm, 2 = 5–10 mm, 3 = 10 mm). A total lesion score was obtained by adding the scores of the various areas examined. A 'periventricular' score was obtained by adding the scores of the periventricular areas, a 'frontal' score by adding the scores of the areas around the frontal horns and those of the frontal lobes, and a 'temporal' score by adding the scores of the areas surrounding the temporal horns to those of the temporal and parietal lobes.

MRI scans were obtained in all those with clinically isolated lesions and in 40 normal controls. In addition, 16 randomly selected physically disabled controls were also scanned as a probe to detect the presence of unsuspected brain pathology. Due to the limited availability of the MRI scanner it was not possible to scan all the subjects in this group.

In most cases the psychometric, psychiatric and motor assessments were carried out on the same day as the MRI scan, but when this was not possible the interval between the clinical and MRI assessments was never more than 2 weeks. The subject's informed consent was obtained in all cases.

Statistical analysis

Nonparametric statistics were used. This decision was taken because some of the variables were not normally distributed and others such as the Cognitive Ability Index were scored on an ordinal scale. Differences between the groups were tested using the Mann-Whitney U test and the Kruskall-Wallis one way analysis of variance (ANOVA). The Kendall tau test was used to explore correlations between variables. Two tailed tests of significance were used throughout. The Statistical Package for Social Scientists (SPSS/PC) (Norušis, 1986) was used for the analysis.

RESULTS

Psychometric results in patients and physically disabled controls

Patients with optic neuritis, brainstem and spinal cord lesions performed similarly in all psychometric tests (Table 1) and for this reason they were considered as a single group for the main analysis. As expected there were no significant differences in age, sex or education between patients with clinically isolated lesions and physically disabled controls. The means and standard deviations for each of the cognitive measures are given in Table 2.

The Cognitive Ability Index of the patients with clinically isolated lesions was significantly different from that of the controls (respective means, 7.15 and 5.3, $P < 0.001$) indicating a worse overall performance on psychometric tests. The specific differences between the groups were explored by comparing the grades obtained on each function (Table 3). Thus while nearly half the controls scored within Cognitive Ability Grade 0 (good performance), less than a quarter of the

TABLE 1. MEAN SCORES IN PATIENTS WITH CLINICALLY ISOLATED LESIONS

	Optic neuritis (*n = 14*)	*Brainstem* (*n = 16*)	*Spinal cord* (*n = 18*)	*Kruskal-Wallis* χ^2
Premorbid IQ (NART)	112.5 (5.7)	111.5 (6.3)	109.0 (8.1)	2.51
Full scale IQ (WAIS)	110.4 (7.5)	106.2 (11.5)	108.1 (10.2)	0.47
Verbal memory	12.9 (1.8)	11.8 (2.8)	12.1 (2.6)	0.66
Visual memory	11.2 (3.2)*	11.6 (2.7)	11.1 (3.0)	0.16
Abstracting ability	5.4 (3.6)	5.7 (3.9)	8.7 (7.6)	1.20
Visual attention	15.8 (2.8)*	14.3 (4.4)	18.0 (7.2)	2.4
Auditory attention	1.3 (1.8)	2.3 (1.5)	2.8 (4.2)	4.03
Naming ability	21.6 (3.7)	21.4 (4.8)	22.6 (3.7)	0.68

* n = 7; SD in brackets.

TABLE 2. PSYCHOMETRIC FUNCTION SCORES IN PATIENTS WITH CLINICALLY ISOLATED LESIONS AND CONTROLS

	Clinically isolated lesion patients (*n = 48*)	*Controls* (*n = 46*)
Premorbid IQ	110.7 (6.9)	109.2 (7.8)
Full Scale IS (WAIS)	108.0 (10.1)	109.7 (9.9)
IQ deficit	2.2 (7.4)	—0.7 (8.4)
Verbal memory	12.1 (2.5)	12.5 (2.0)
Visual memory	11.3* (2.9)	12.0 (3.4)
Abstracting ability	6.7 (5.6)	5.8 (5.2)
Visual attention	16.2* (5.4)	14.1 (3.4)
Auditory attention	2.2 (2.9)	1.2 (2.1)
Naming ability	21.9 (4.0)	21.7 (3.0)

* n = 41; SD in brackets.

patients did so, and the patients were three times as likely as the controls to score within Grade 3 (deficient range) (*see* fig.). In addition, the distribution of patients and controls across the grades was significantly different for IQ deficit, and for visual and auditory attention (Table 3).

Clinical features and psychometric test performance

Duration of illness. The controls had been ill for longer than those with clinically isolated lesions (mean duration of illness 9.3 and 2.2 yrs, respectively, $P < 0.001$). Within the clinically isolated lesion group, 38 of the 48 patients had had symptoms for less than a year; only 1 had been affected for longer than 4 yrs. The mean duration of illness was shortest for those with optic neuritis (mean 0.93 yrs), followed by those with brainstem (2.5 yrs) and cord lesions (3 yrs). These differences between groups reached statistical significance ($P < 0.04$).

In the control group the duration of illness was not significantly related to the performance on any of the psychometric tests. In the clinically isolated lesion

TABLE 3. PSYCHOMETRIC FUNCTION GRADES IN PATIENTS WITH CLINICALLY ISOLATED LESIONS AND CONTROLS

	Grades (% in each group)								
	0 (good)		*1 (fair)*		*2 (poor)*		*3 (deficient)*		*Mann-Whitney Z*
	Patients	*Controls*	*Patients*	*Controls*	*Patients*	*Controls*	*Patients*	*Controls*	
IQ deficit	33	54	27	28	29	13	10	4	−2.45*
Verbal memory	54	61	19	20	23	17	4	2	−0.80
Visual memory	40	52	33	28	25	13	2	7	−1.11
Abstracting ability	42	52	29	24	27	22	2	2	−0.93
Visual attention	27	52	38	26	27	17	8	4	−2.33*
Auditory attention	25	48	23	30	44	20	8	2	−3.02**
Naming ability	52	37	23	30	15	20	10	2	−1.08

* $P < 0.05$; ** $P < 0.005$.

group as a whole there was a significant correlation between the duration of neurological symptoms and the performance on visual attention tests ($P < 0.05$), and within this group the most significant correlations were found in those with spinal cord lesions who also had the longest duration of symptoms. Thus the longer the history the greater the impairment in tests of Visual Attention ($P < 0.02$), Auditory Attention ($P < 0.02$), Abstracting Ability ($P < 0.04$), and Cognitive Ability Index ($P < 0.05$).

Physical disability. Within the clinically isolated lesion group, impairment in tests of attention could not be explained as a result of the neurological deficits. Optic neuritis patients with impaired vision were excluded, and those with brainstem syndromes performed the same as the remainder of the group in tests of Auditory Attention (Table 1). Physically disabled controls performed significantly worse than the patients with clinically isolated lesions in Activities of Daily Living ($P < 0.05$). Similarly, within the clinically isolated lesion group those with optic neuritis performed significantly better than the rest on these

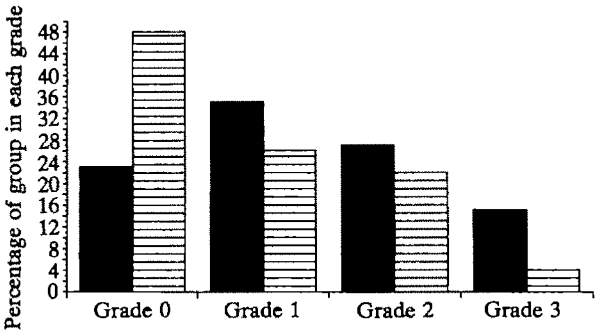

FIG. Cognitive ability grades for clinically isolated lesion group (filled areas) and physically disabled controls (hatched areas).

complex activities ($P < 0.005$), even though the group as a whole was only mildly disabled.

There were no differences between the patients with clinically isolated lesions and the physically disabled controls in the test of hand function. Performance on this test was also similar across the 3 subgroups of patients with clinically isolated lesions. Within the clinically isolated lesion group significant correlations were found between the speed of hand function and the scores of the psychometric tests with the exception of tests of memory and naming ability. In the physically disabled control group significant correlations, albeit with a different pattern, were also found. Thus Visual Memory ($P < 0.05$), Naming Ability ($P < 0.05$) and Cognitive Ability Index ($P < 0.005$) became worse as hand speed decreased.

Relapses and remissions. The 17 patients who were in relapse at the time of the study had significantly greater IQ deficit than the rest of the group ($P < 0.05$), the individual psychometric functions and overall Cognitive Ability were similar in both groups.

Psychiatric morbidity. Eight of the 48 patients with clinically isolated lesions were considered to have clinically significant psychiatric symptoms at interview, while this was the case for 2 of the 46 physically disabled controls. These differences failed to reach statistical significance, and the same was true for the CIS scores in each group (Mann-Whitney $Z = 0.43$, $P = 0.67$).

In the clinically isolated lesion group there were no significant differences in the psychometric test performance between those who were psychiatrically ill and the rest. In the group as a whole the severity of psychiatric symptoms, as reflected in the CIS score, correlated significantly with the Cognitive Ability Index and Visual Attention scores, while in the control group similar correlations were obtained with the measure of IQ deficit and the Cognitive Ability Index (Table 4).

Abnormal fatiguability. The subjective experience of fatigue was one of the symptoms rated in the CIS. Patients who scored 2 or more (range 0–4) were considered to be abnormal. Thirteen of the 48 patients with clinically isolated lesions and 11 out of the 46 controls were found to have abnormal fatigue ratings.

TABLE 4. PSYCHIATRIC MORBIDITY AND PSYCHOMETRIC TEST PERFORMANCE

Correlations with CIS score (Kendall tau)	*Patients ($n = 48$)*	*Controls ($n = 46$)*
IQ deficit	0.05	0.18*
Verbal memory	−0.002	0.00
Visual memory**	−0.008	−0.02
Abstracting ability	0.14	0.08
Visual attention**	0.25*	0.14
Auditory attention	0.09	0.16
Naming ability	0.14	0.15
Cognitive ability index	0.20*	0.19*

* $P < 0.05$; ** $n = 41$; CIS = Clinical Interview Schedule.

In the clinically isolated lesion group those with abnormal ratings had significantly worse Abstracting Ability functions ($P < 0.05$) and a worse Cognitive Ability Index ($P < 0.05$) when compared with the rest of the group, while in the control group greater IQ deficit ($P < 0.05$), worse Visual Attention ($P < 0.05$) and Cognitive Ability Index ($P < 0.05$) were the main differences.

Psychotropic drugs. There were no significant differences in the performance of psychometric tests between patients with clinically isolated lesions who were receiving psychotropic medication and those who were not. The same was the case for the physically disabled controls.

MRI abnormalities in patients and controls

The MRI abnormalities in patients and controls have already been reported elsewhere (Logsdail *et al.*, 1988). Abnormalities were detected in 39 of the 48 patients with clinically isolated lesions (81%) and in 2 of the 16 physically disabled controls. The proportion and type of abnormalities detected in the physically disabled controls were similar to those found in the normal controls, in whom abnormalities were present in 5 out of 40. In those with clinically isolated lesions a periventricular rim of increased signal was the commonest MRI abnormality, often accompanied by discrete lesions in the brain parenchyma. The total lesion score of the group with clinically isolated lesions was significantly different from those of the 2 control groups (total lesion scores 9.8, 0.71 and 0.52, respectively; ($P < 0.001$). There was no significant difference in the total lesion score between the clinically isolated lesion subgroups, but in those with cord lesions the score was significantly correlated to the duration of neurological symptoms ($P = 0.02$).

Psychometric tests and MRI abnormalities

Of the individual psychometric functions explored, performance in tests of auditory attention and abstracting ability were significantly correlated with the total lesion score (Table 5). A similar trend was also found for those with more

TABLE 5. MRI TOTAL LESION SCORE AND PSYCHOMETRIC FUNCTION SCORES IN PATIENTS WITH CLINICALLY ISOLATED LESIONS

	MRI total lesion score (Kendall tau)
IQ deficit	0.11
Verbal memory	−0.02
Visual memory	0.07
Abstracting ability	0.18*
Visual attention	0.01
Auditory attention	0.20*
Naming ability	−0.03
Cognitive ability index	0.16

* $P < 0.05$.

MRI abnormalities to have a poorer overall Cognitive Ability Index, although this correlation failed to reach statistical significance. Furthermore, when those with a Cognitive Ability Grade of 0 (good performance) were compared with those who scored within Grade 3 (deficient performance) the degree of detectable brain pathology was different in the 2 groups. Thus the total lesion score was 3 times higher for those in Grade 3 than for those in Grade 0 (means 21.1 and 6.7; $P < 0.05$).

There were no significant correlations between the results of the psychometric tests and the 'periventricular', 'frontal', and 'temporal' scores.

The 2 physically disabled controls with MRI abnormalities (aged 51 and 62 yrs) were older than the mean age for the group (39 yrs). One of them suffered from a prolapsed intervertebral disc and the other had a neurofibroma of a spinal root. Their scores on the Cognitive Ability Grade were 1 and 2, respectively.

DISCUSSION

We report here a study of the psychometric deficits encountered in a group of patients with clinically isolated lesions of the type seen in MS in whom the presence of brain pathology has been ascertained by MRI. The results of the study suggest that cognitive impairment can be detected when other manifestations of brain pathology are absent and that attention deficits are the most prominent cognitive abnormalities in these patients. These deficits are related to the duration of the neurological symptoms and are significantly correlated with the overall degree of brain pathology detected using MRI.

The control group used in the study differed from the group with clinically isolated lesions in several important ways and this illustrates the difficulties encountered in trying to match subjects for all the relevant variables. The physically disabled patients had been ill for longer and had greater physical handicaps than those with clinically isolated lesions. However, the speed of hand function, a measure relevant to the performance of psychometric tests, was similar in the 2 groups. These differences could hardly explain the worse cognitive performance in those with clinically isolated lesions, and if at all relevant they are likely to minimize the differences in test performance between the 2 groups.

The presence of psychiatric symptomatology is also unlikely to account for the greater cognitive impairment in those with clinically isolated lesions. Psychiatric morbidity was low in both groups and was found to be more closely related to environmental factors than to the presence of brain pathology (Logsdail *et al.*, 1988). The modest correlations found between the severity of psychiatric symptoms and cognitive performance were present in patients and controls, and therefore are unlikely to account for the cognitive differences between the groups.

Abnormal fatiguability, a common complaint in definite MS, is believed in most cases to be a primary manifestation of the disease, although in some patients it could be a symptom of depression, systemic illness or a side-effect of drugs. In our study, patients with clinically isolated lesions complained of fatigue as often as controls, even if the use of psychotropic medication was the same in both groups and unrelated to test performance. This suggests that fatiguability in the clinically isolated lesion patients, who are less disabled than controls, is partly due to the presence of brain damage. On the other hand, fatigue per se is unlikely to account for the differences in cognitive ability between the 2 groups.

In the only available study of cognitive impairment in patients with clinically isolated lesions, Lyon-Caen *et al.* (1986) have described cognitive impairment in those with optic neuritis when compared with a heterogeneous group of patients, some of whom were likely to have been brain damaged. Their findings are in some way similar to those reported here, although the relationship of cognitive impairment to brain pathology was not explored in that study.

In comparison with patients suffering from definite MS, the cognitive deficits of our patients with clinically isolated lesions are mild. A variety of memory functions, free recall in particular, have been found to be impaired in MS even after a short illness (Grant *et al.*, 1984; Rao *et al.*, 1984). Recognition memory tests were used in our study because they allow the testing of visual and verbal memory using the same technique, something difficult to achieve with tests of free recall, and because they are resistant to the effects of depression (Coughlan and Hollows, 1984). No memory disturbances were found using these tests in our patients, but it would be worthwhile to examine memory functions in greater detail in future studies, as they are likely to be affected early in the course of the disease. The normal performance in tests of naming ability is in keeping with the well preserved language abilities often reported in patients with definite MS. On the other hand, there was a suggestion that a decline in IQ may have been present in some of our patients, an observation also reported in those with definite MS (Hirschenfang and Benton, 1966; Reitan *et al.*, 1971).

Attentional processes have not been explored in patients with definite MS, despite empirical reasons to suspect that they may be impaired in a disease with predominantly subcortical pathology. Moreover, attention is required in the performance of tasks of abstracting ability known to be impaired in definite MS (Parsons *et al.*, 1957; Reitan *et al.*, 1971; Ivnik, 1978). In our study measures of auditory and visual attention were impaired in patients with clinically isolated lesions whose performance on a number of other tests was normal, suggesting that this may be one of the most sensitive measures of cognitive impairment in MS.

The cognitive impairment in patients with clinically isolated lesions was best illustrated by the use of the Cognitive Ability Index. By combining the various test scores this overall measure highlights the presence of minor degrees of impairment that would have remained undetected if only single test measures had been used, and removes the need for making multiple comparisons which could have yielded spurious results.

The MRI abnormalities found in this study have been described in detail elsewhere (Logsdail *et al.*, 1988). Briefly, the proportion of MRI abnormalities found in the physically disabled patients was similar to that found in the normal control group and in keeping with previous studies of healthy volunteers (Gerard and Weisberg, 1986; D. Miller, personal communication, 1987), which have reported the increasing frequency of patchy periventricular high signal lesions with advancing age. The type and distribution of MRI abnormalities in the patients with clinically isolated lesions were similar to those found in definite MS, but the overall amount of detectable pathology was much smaller. In our study, the most striking cognitive abnormality, impaired auditory attention, was also the one which correlated most closely with the overall degree of detectable brain pathology, followed by impairment in abstracting ability, a function which is partly dependent on attentional processes. These clinicopathological correlations were also reflected in the significantly greater degree of brain pathology detected in those with a deficient overall Cognitive Ability when compared with those with good overall performance. The lack of correlation between the specific functions tested and the indices of focal brain pathology was disappointing. However, these are crude indicators of the extent of MRI abnormalities in large brain regions and it is likely that more accurate delimitation of areas involved in specific cognitive processes and the use of more sensitive magnetization parameters will yield more relevant information.

Finally, the results of the study suggest that in patients with clinically isolated lesions cognitive impairment is a more reliable indicator of brain pathology than the presence of psychiatric abnormalities (Logsdail *et al.*, 1988) or more conventional neurological symptoms or signs. It would also seem possible that in cases of 'silent' or 'benign' MS (Gilbert and Sadler, 1983), similar abnormalities might have been elicited if carefully explored.

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EVIDENCE FOR A CONTRIBUTION OF THE AUDITORY CORTEX TO AUDIOSPINAL FACILITATION IN MAN

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SUMMARY

Facilitation of the spinal monosynaptic reflex by auditory stimulation has been demonstrated previously in animals and man. Analysis of the time course of audiospinal facilitation (ASF) in normal subjects is reported. The role of the cerebral cortex in the control of audiospinal facilitation was investigated in 32 patients with anatomically well-circumscribed lesions, the precise topography of which was determined stereotaxically. Lesions of the caudal part (Heschl's gyrus and temporal plane) of the superior temporal gyrus selectively depressed ASF evoked by contralateral auditory stimulation. In contrast, lesions in temporal, parietal and occipital lobes had no effect. Results obtained with frontal lobe lesions were not homogeneous. The specific involvement of auditory cortex in the gating of behavioural audiomotor reactions is discussed.

INTRODUCTION

Sound-induced variations in the amplitude of the H reflex are known to exist from the studies of Davis *et al.* (1955) and Davis and Beaton (1968). Paillard (1955) and Melvill-Jones *et al.* (1973) described the time course of this increase in spinal excitability which begins 50 ms after the onset of an acoustic stimulus, has a duration of 200 ms, and reaches peak amplitude 100 ms after stimulus onset. The audiospinal facilitation (ASF) could be considered as underlying audiomotor mechanisms (e.g., in dancing, Rossignol and Melvill-Jones, 1976). It has more often been considered as a measurable physiological substrate of the startle reaction preferentially induced by auditory stimuli and manifested in the soleus muscle at a latency close to the maximum audiospinal facilitation (Rossignol, 1975). The use of more intense acoustic stimulus can induce an overt startle response, as confirmed by Rudell and Eberle (1985).

The pathways involved in production and control of the startle reaction have been explored much more frequently in animals than in man. Since the observations of Forbes and Sherrington (1914) in decerebrate cats, a number of animal

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experiments performed in various preparations have established that the startle pattern depends on the activation of subcortical circuits involving the inferior colliculus and the bulbar reticular formation (Ascher, 1965; Buser *et al.*, 1966; Hammond, 1973; Groves *et al.*, 1974; Willott *et al.*, 1979; Leitner *et al.*, 1980). Most of these studies have indicated that auditory pathways rostral to the inferior colliculus are not required for acoustic startle. In awake rats, Groves *et al.* (1974) showed that lesions of the inferior colliculus reduced but did not abolish the acoustic startle reflex. In man, Gogan (1970), in an analysis of the EMG response to an acoustic stimulus, proposed that the early component of the startle reaction might be generated by structures probably located in the bulbar reticular formation. Similar conclusions were reached by Shimamura (1973) studying children with cerebral palsy.

The role of the cerebral cortex remains a matter of controversy. It is known that patients with extensive cortical lesions exhibit an exaggerated startle reflex (Wilkins *et al.*, 1986) with a decrease in its habituation (Briullova, 1958; Bronstein *et al.*, 1958; Shimamura, 1973). Such data have led to the general opinion that the cerebral cortex, taken as a whole, could have an inhibitory influence on this reaction. On the other hand, Woods *et al.* (1984) and Ho *et al.* (1987) stated that bilateral temporal lobe lesions including the auditory cortex abolished the startle reflex. In the same way, Ascher (1965) then Buser *et al.* (1966) reported that in chloralose anaesthetized cats, ablation of a cortical primary sensory area (visual, auditory or somaesthetic) reduced the startle response induced by the same sensory modality stimulation. They concluded that these areas have a 'specific' facilitatory influence on the startle reaction.

The present study was undertaken to investigate whether the auditory cortex has a role in the control of ASF in man. It was performed in patients with well-circumscribed lesions of the cerebral cortex exploiting the precise knowledge of the anatomical location of these cortical lesions reliably obtained by means of the stereotactic neuroradiological methods developed by Talairach and Szikla (Talairach *et al.*, 1967; Szikla *et al.*, 1977).

PATIENTS AND METHODS

Experiments were performed on 9 healthy adult volunteers (5 right-handed and 4 left-handed, aged 20–45 yrs) and 32 patients. Patients were selected on the basis of having well-circumscribed lesions in one cerebral hemisphere. They were chosen from the population of epileptic patients referred to the Neurosurgical Department, Hôpital Sainte Anne, Paris, as candidates for surgical therapy of their seizures. Before surgery, these patients underwent a stereoelectroencephalographic exploration (SEEG), the methodology of which has been extensively described elsewhere (Bancaud *et al.*, 1965; Talairach *et al.*, 1974). Patients were informed of the experimental aim of the study and gave their consent to the procedure.

Stereotaxic method for anatomical localization

The successive explorations are based on an unique stereotaxic method where the clinical seizure patterns, the physiological data and the radiological delineation of the lesion are all consistently referred to their anatomical correlates. Thus the extent of the corticectomy is decided specifically for each patient and is entirely preprogrammed.

In order to get a precise localization of the cerebral structures, the following explorations are performed. After positioning in Talairach's stereotactic frame, the patient undergoes a neuroradiological investigation (unilateral or bilateral carotid angiography, ventriculography). Teleradiographic stereoscopic angiography is performed in each case. The resulting undistorted, real size, stereoscopic radiographs give a precise representation of the vascular tree. In this way the three-dimensional angiography can provide an 'in vivo' localization of cortical sulci and gyri (Szikla *et al.*, 1977). The anatomical substratum of this statement is the intimate adherence of arteries (and to a lesser extent veins) to the free buried cortical surface during embryonic development. Convexities and concavities, gyri and sulci of the cortical surface are moulded by the vascular envelope, the tortuosity of cerebral vessels reflecting the shape of the underlying cortex. Taken together, the deep segments of arteries and veins, running on the infolded cortical surface of a sulcus, form a vascular lamina corresponding to and outlining the topography of the sulcus. The stereoscopic visualization of these deep segments provides a precise and direct localization of the different structures of the cerebral cortex (for instance, superior temporal gyrus, Heschl's gyrus, temporal plane).

The positive double contrast ventriculography visualizes the anterior (AC) and posterior (PC) commissures, permitting a trace of the bicommissural (AC-PC) reference stereotactic baseline. A proportional grid based on the AC-PC line constitutes a common denominator for all individuals, whatever their cerebral dimensions (Talairach *et al.*, 1967). Surgical excisions are preprogrammed with respect to coordinates within the three-dimensional image. This knowledge of the precise anatomical localization of the lesion could be verified by MRI examination in some patients.

Patients were divided into 3 groups: (1) 12 had a superior temporal gyrus (STG) lesion including or limited to Heschl's gyrus; (2) 9 had a temporal lobe lesion excluding Heschl's gyrus; (3) 11 had a nontemporal lobe lesion, 6 with frontal lobe lesions and 5 with parietal and/or occipital lesions. The classification of patients with reference to the different types of investigation to which they were submitted in order to make a topographic diagnosis of their lesions is given in the Appendix, together with the results of neurological examination. In all patients, the tendon reflexes were symmetric in the lower limbs. Fig. 1 illustrates the anatomical localization of lesions in Talairach's system; they are grouped according to the three above mentioned categories and correspond to the individual cases whose neurophysiological data will be further considered. In the first group the lesions were much more restricted in size than in the others.

Neurophysiological methods

H reflexes. The size of the soleus H reflex was used to assess the effect of the conditioning auditory stimuli. The H reflex was obtained by stimulating the tibial nerve in the popliteal fossa through monopolar surface electrodes with 1 ms rectangular constant current pulses delivered by a Disa stimulator. The strength of the test reflex was equal to about 15% of the maximum motor response (M_{max}) in control conditions. The reflex responses were measured by an EMG recording with a pair of surface electrodes placed 1 cm apart over the soleus distal to the gastrocnemius.

Auditory stimulation

Monaural auditory stimuli presented through TDH 39 earphones were generated by a Nicolet SM 700 stimulator and consisted of 750 Hz tone bursts with a plateau duration of 30 ms and a rise and decay time of 0.3 ms. The auditory threshold level was determined for each subject; the intensity of the acoustic stimulus was 85 dB above this threshold, expressed in dB HL (hearing level).

Audiograms performed in each patient indicated that pure tone thresholds in both ears ranged between 30 and 40 dB HL across test frequencies. In some patients (Cases 1, 2, 3, 6), we observed a loss of 5-10 dB for the ear contralateral to the lesion which was not significant. Brainstem auditory evoked potentials (BAEPs) were normal.

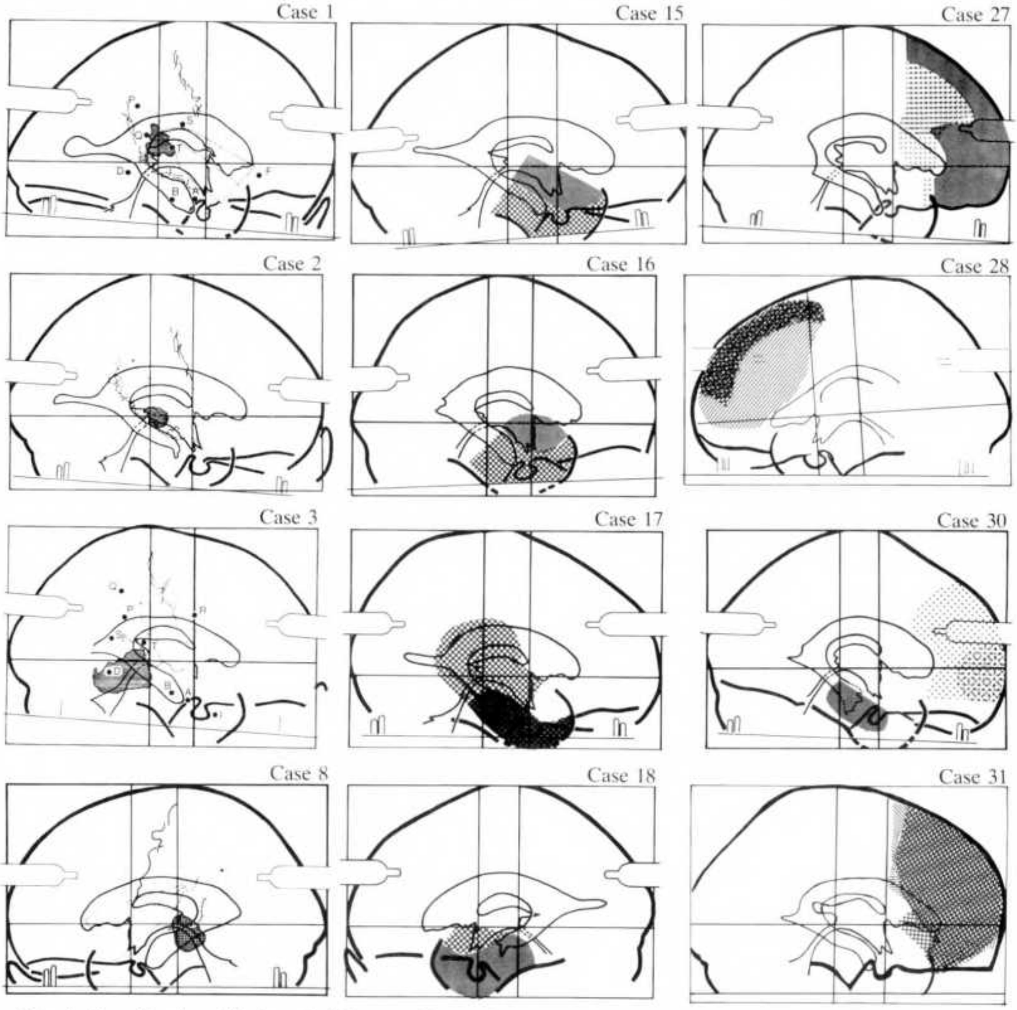


FIG. 1. Localization of lesions in 12 cases. *First column*: 3 patients with temporal lobe lesions (shaded areas) localized in the posterior part of the superior temporal gyrus (*Cases 1, 2, 8*) and 1 patient (*Case 3*) whose lesion is situated in the posterior part of middle and inferior temporal gyri spreading into centrotemporal white matter, completely disconnecting the posterior part of the superior temporal gyrus; unbroken lines = rolandic arteries; dotted lines = insular triangle; dashed lines = inferior and posterior limits of superior temporal gyrus; letters = position of depth electrodes implanted for SEEG. *Second column*: 4 cases of temporal corticectomy, sparing Heschl's gyrus (*see* Appendix); solid shading = medial corticectomy; cross-hatched area = lateral corticectomy. *Third column*: 4 cases of frontal corticectomy; in *Case 30*, there was an associated temporal corticectomy.

Experimental procedure

The time course of soleus H reflex variations after acoustic stimulation was studied by delaying the H reflex triggering by various time intervals from the auditory stimulus. Time intervals from 40 to 200–250 ms were explored. This means that the delay between the onset of the auditory stimulus and the appearance of the H reflex in the soleus EMG varied approximately from 70 to 230–280 ms since the H reflex appears about 30 ms after the electrical stimulation.

The soleus H reflex evoked in control conditions was randomly alternated with the conditioned reflex. The type of auditory stimulation and the mode of alternation of control and conditioned test reflexes was determined by a Nicolet Pathfinder II programmed by the experimenter before each experimental series.

The ratio of conditioned versus nonconditioned reflex amplitude was used as a measure of the effect of the auditory stimulation on the modification of the excitability of monosynaptic soleus reflex. A parametric statistical analysis (Student's t test) was used to test the significance of the variations in reflex amplitude.

The experiments were performed on both the right and left soleus H reflex in each patient. In some of them, audiospinal facilitation was studied twice, before and after corticectomy (*see* Appendix, where the anatomical lesion at the time of neurophysiological investigation is given).

RESULTS

Time course variations in the soleus H reflex after auditory stimulation in normal subjects

Fig. 2 shows the typical time course variations in the soleus H reflex after a monaural auditory stimulation. The tone bursts (750 Hz, 85 dB HL) caused a facilitation of the reflex. The minimum effective conditioning test interval was 60 ms; the test reflex was maximally facilitated at an interval of 100–120 ms and returned to control level after an interval of 200–250 ms. Both left (dotted line) and right (continuous line) ear stimulation curves were superimposable.

As an ear dominance has previously been reported in tone recognition (Efron *et al.*, 1983), more or less closely related to manual preference (Hécaen, 1984), we

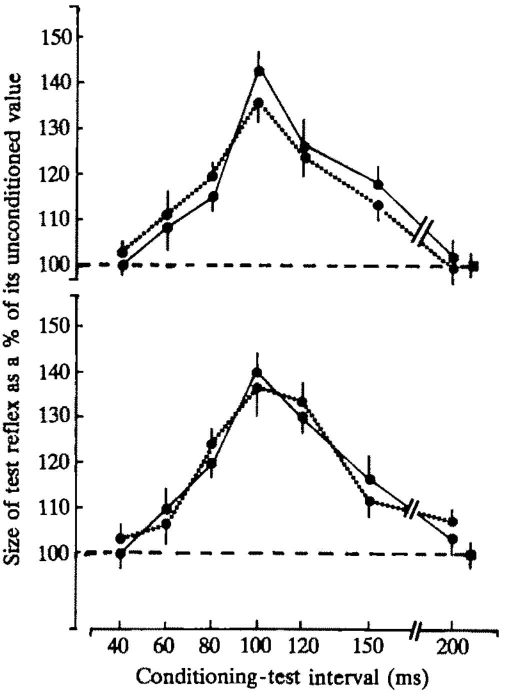


FIG. 2. Time course of variations in the soleus H reflex after auditory stimulation in normal subjects. *Top*, right-handed subjects; *bottom*, left-handed subjects; filled circles = stimulation of right ear; open circles = stimulation of left ear. Each symbol represents the mean value obtained from 5 right-handed subjects and 4 left-handed subjects. Vertical bars = SEM; filled squares = mean amplitude of test reflex. Tone bursts 750 Hz, 85 dB HL.

explored right and left-handed subjects. The same effects were obtained in the 5 right-handed subjects (fig. 2, top) as in 4 left-handed subjects (fig. 2, bottom). The side of the ear stimulation did not influence the time course of the reflex. Experiments were performed on the right and left soleus H reflexes. The results were identical, regardless of side stimulated.

Time course variations in the soleus H reflex in patients with temporal lobe lesions including Heschl's gyrus

In fig. 3 (left) examples of H reflex facilitation in 3 patients with right temporal lobe lesions are presented. Stimulation of the left ear (contralateral to the lesion)

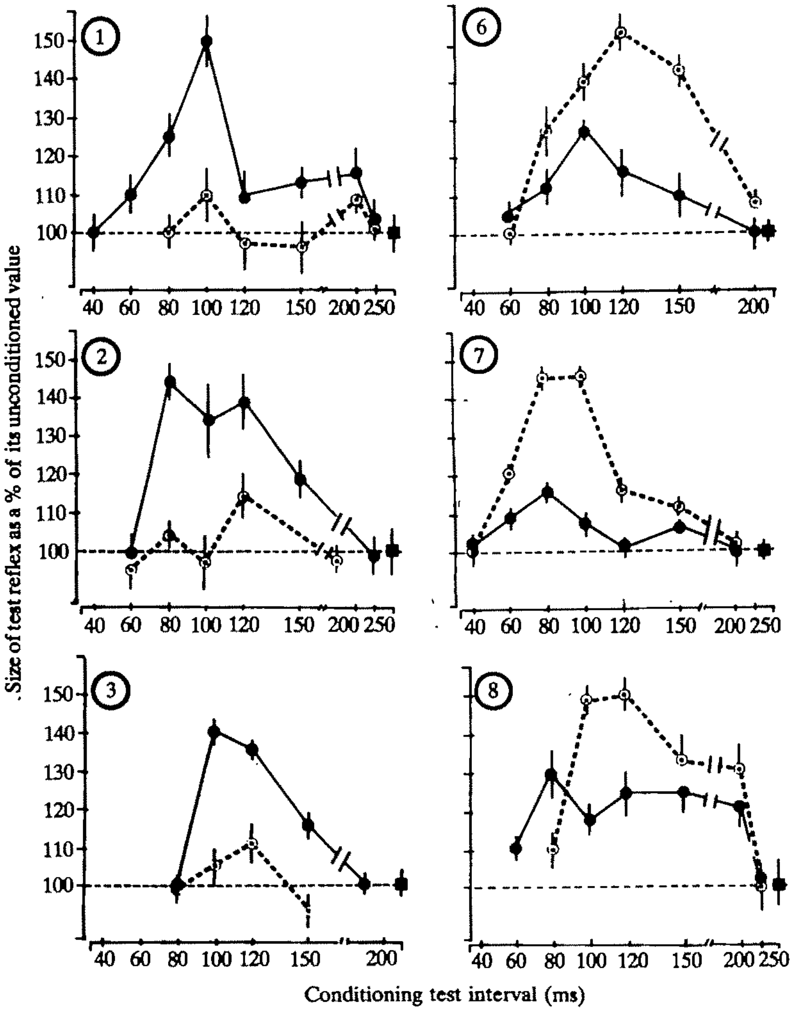


FIG. 3. Time course of variations in the soleus H reflex in 6 cases with lesions of the superior temporal gyrus (*see* fig. 1, Appendix 1). *Left*: right temporal lobe lesions (*Cases 1, 2, 3*); unbroken line = right ear stimulation; dashed line = left ear stimulation. *Right*: left temporal lobe lesions (*Cases 6, 7, 8*). Description as in fig. 2.

did not give rise to any facilitation (dashed line). In contrast, right ear stimulation provoked facilitation similar to that observed in normal subjects.

The same experiments were performed in subjects with left temporal lobe lesions, and here too the stimulation of the ear (right) contralateral to the lesion produced a weaker facilitation than that evoked by stimulation of the ear (left) ipsilateral to the lesion (fig. 3, right). The difference in facilitation curves for right ear versus left ear stimulation was statistically significant ($P < 0.05$).

In all 12 patients in this group an asymmetry of audiospinal facilitation was present. H reflex amplitude was insensitive or less sensitive to auditory stimuli when they were delivered to the ear contralateral to the patient's cerebral lesion. In contrast, stimulation of the ipsilateral ear induced H reflex facilitation as in the control subjects.

Patients with left superior temporal gyrus lesions only showed a significant decrease of ASF when stimulation was given to the right ear, and not total abolition, as was observed in patients with lesions of the right superior temporal gyrus. As the number of patients is too small for statistical analysis, this difference cannot be definitely related to hemisphere dominance.

In order to elucidate whether depression of ASF was confined to lesions of the auditory cortex, audiospinal facilitation was also studied in patients with lesions outside Heschl's gyrus.

Time course of variations in the soleus H reflex after acoustic stimulation in patients with lesions outside Heschl's gyrus

Temporal lobe lesions (*6 patients*). In patients with temporal lobe lesions outside the caudal part of the superior temporal gyrus, there was no evidence for the asymmetry described above. In fig. 4, data from 4 patients whose lesions were localized to other parts of the right or left temporal lobe (*see* Appendix) are presented. The H reflex facilitation was observed with the same amplitude and latency as in normal subjects whether the tone burst was delivered to the right or left ear.

Parietal and occipital lobe lesions (*5 patients*). No abnormality or asymmetry in H reflex facilitation was observed for lesions in these situations.

Frontal lobe lesions (*6 patients*). Six subjects were studied. The results obtained were not uniform (fig. 5). In 3 patients, there was no asymmetry in audiospinal facilitation. For example, in Case 31, the two facilitation curves were symmetric. In Case 30, a patient with a right temporofrontal corticectomy, there was no reduction in the facilitation produced by left ear stimulation compared with right ear stimulation (the difference between the two curves—right and left ear stimulation—is not significant).

In 3 other patients, the results observed were similar to those recorded in subjects with a temporal lobe lesion localized in Heschl's gyrus. In 1 patient with a left-sided lesion (Case 28), we observed that right ear stimulation provoked only weak facilitation, and in 1 patient with a right frontal lesion (Case 27), no facilitation on left ear stimulation was observed.

Role of epileptogenic versus nonepileptogenic lesion on audiospinal facilitation

As the majority of the present experiments had been obtained in epileptic patients with a cortical lesion, it appeared important to distinguish between the possible effects of localized interictal discharges and of the lesion itself. A further series of experiments was therefore performed in 4 patients after corticectomy. Although they were seizure free (Cases 1, 3, 4, 5), the same results were obtained as in the experiments before corticectomy.

Two nonepileptic patients were also studied. In Case 11, where typical ASF asymmetry was noted suggesting a lesion of the auditory cortex, an MRI scan was performed (fig. 6). This demonstrated a spherical defect in Heschl's gyrus. In Case 12 who had a vascular lesion localized in the right auditory cortex (*see* Appendix, part 1) an asymmetry in the H reflex facilitation was also observed.

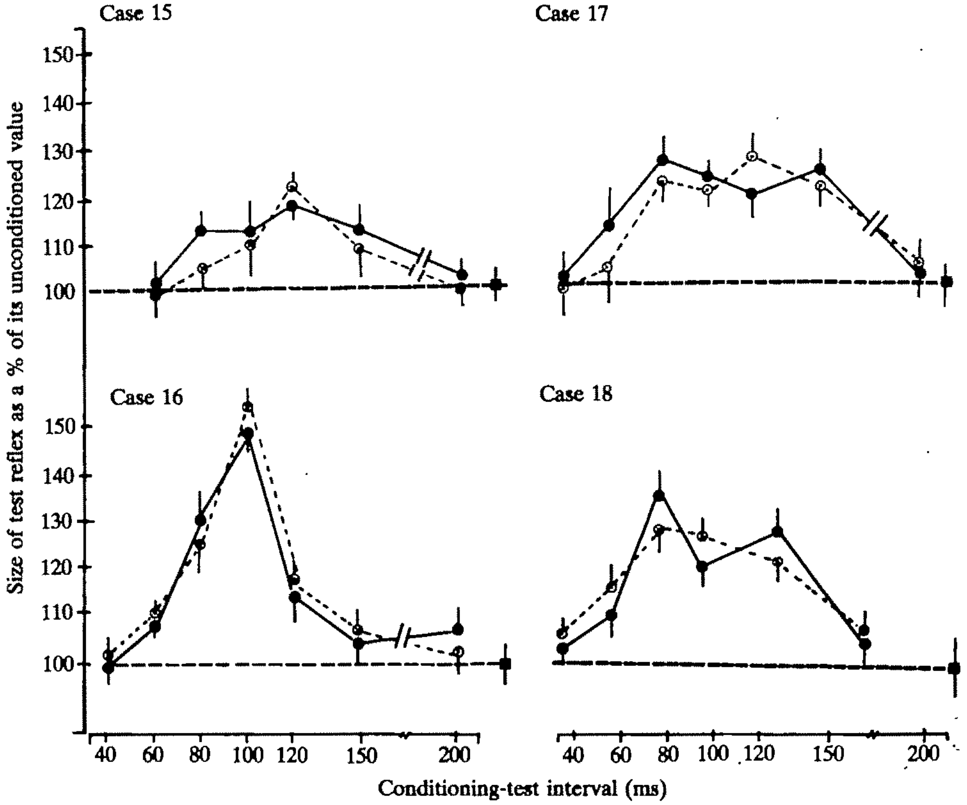


FIG. 4. Time course of variations in the soleus H reflex after auditory stimulation in 4 patients with temporal lobe lesions sparing superior temporal gyrus (*see* fig. 1 2nd column and Appendix 2). Description as in fig. 2.

DISCUSSION

Audiospinal facilitation (ASF) appears to be a general effect of sound on excitability of the monosynaptic reflex arc. The time characteristics of our results in normal subjects do not differ from previous data (Paillard, 1955; Rossignol, 1975; Rudell and Eberle, 1985) obtained for the lower limbs. The facilitation is bilateral, there is no difference in the time course of the soleus H reflex, regardless of which ear is stimulated, and it is symmetrically distributed. This facilitation may be due to an increase of soleus motoneurons excitability and/or to a decrease in presynaptic inhibition acting on soleus Ia fibres.

In 32 patients with unilateral cerebral lesions the effect of auditory stimulation on the soleus H reflex was investigated as a function of the stimulated side. In 21 cases, the effect of lesions of different structures within the temporal lobe was investigated. It must be pointed out that the audiological tests (audiograms and BAEPs) performed in each patient were normal, indicating that the peripheral

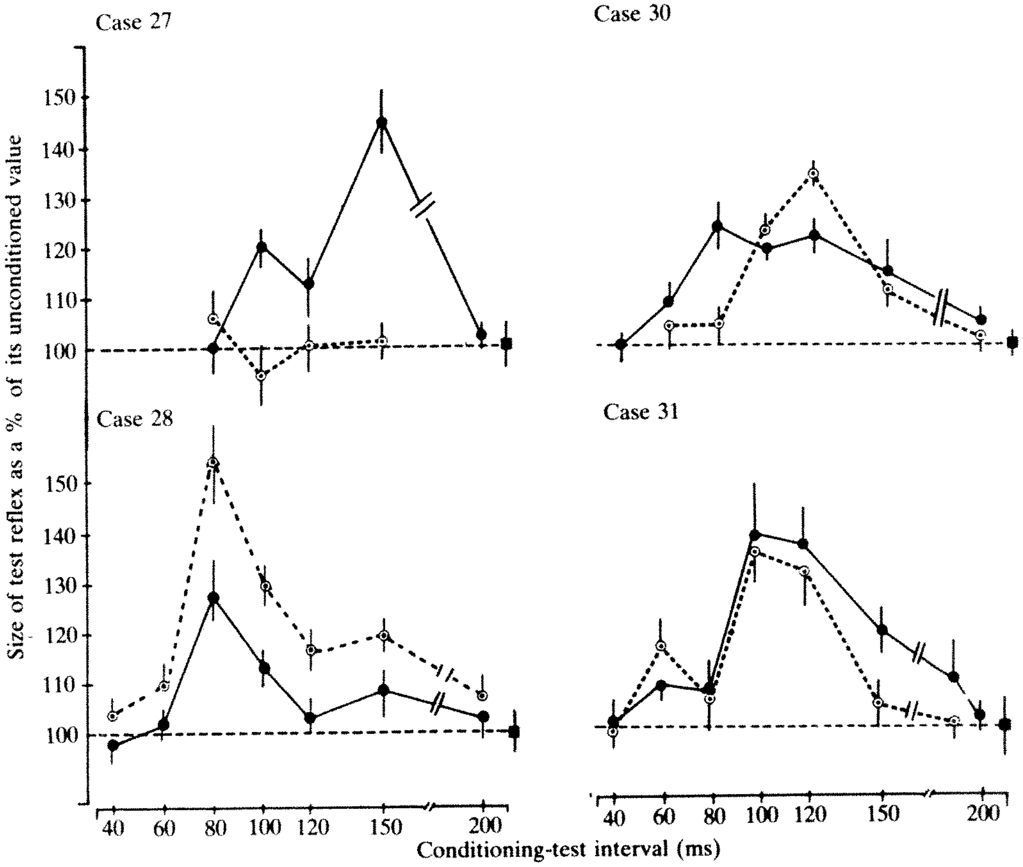
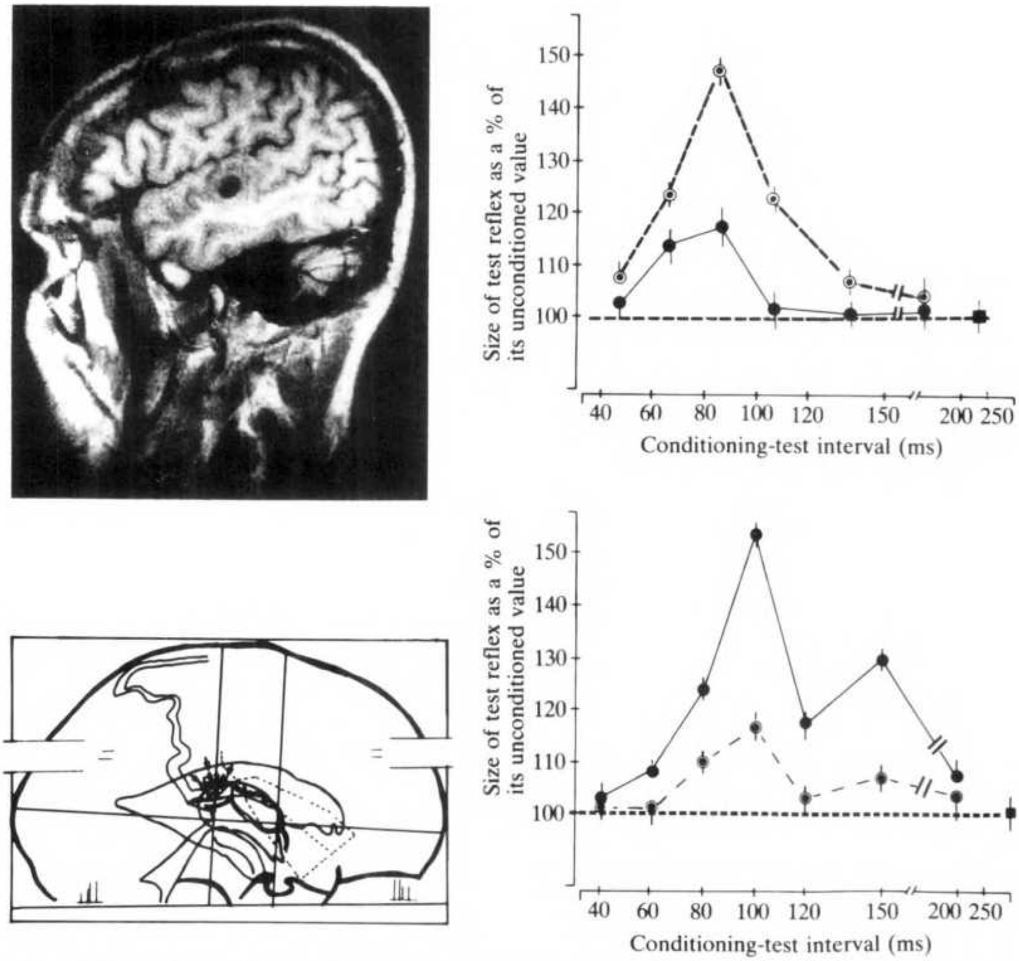


FIG. 5. Time course of variations in the soleus H reflex after auditory stimulation in 4 patients with frontal lobe lesions (*see* fig. 1, 3rd column and Appendix 3). Description as in fig. 2.

hearing apparatus was intact. Only lesions of the superior temporal gyrus were found definitely to influence ASF. Moreover, only lesions posterior to the transverse temporal sulcus resulted in a unilateral decrease of ASF contralateral to the lesion. One apparent exception was noted in Case 3 whose lesion was localized to the posterior part of middle and inferior temporal gyri: it resulted in the same phenomenon. However, the lesion extended into the temporal white matter completely disconnecting the posterior part of the superior temporal gyrus.

Thus only patients with temporal lobe lesions posterior to the transverse gyrus


150
140
130
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Size of test reflex as a % of its unconditioned value
40 60 80 100 120 150 200 250
Conditioning-test interval (ms)
150
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130
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100
Size of test reflex as a % of its unconditioned value
40 60 80 100 120 150 200 250
Conditioning-test interval (ms)

FIG. 6. Two patients with nonepileptogenic lesions in Heschl's gyrus. *Top left*: T1 weighted MRI, superficial sagittal cut, thickness 7 mm, showing round regular hypodensity in the posterior portion of the left superficial temporal gyrus (*Case 11*). The variations in the time course of soleus H reflex after a tone burst are presented top right. *Bottom left*: scheme for stereotactic neuroradiological study in *Case 12*. Arrows show the arteriovenous angioma in the posterior portion of the right superior temporal gyrus. *Bottom right*: time course of variations in the soleus H reflex after auditory stimulation. Description as in fig. 2.

display an asymmetry in ASF. In patients with parietal, parieto-occipital and occipital lesions, no difference was detected in the ASF as compared with control subjects. But the results were not so homogeneous in patients with frontal lobe lesions. In 2 patients (Cases 27, 28) who both had had a large frontal corticectomy (*see* Appendix, part 3; fig. 1), no facilitation was obtained when the ear contralateral to the lesion was stimulated. In contrast, in Case 31, with a lesion of the medial and lateral premotor area, no modification was observed. A further discussion of the effects of frontal lobe lesions will be given below.

The localization of the structures responsible for this facilitatory control will now be considered. In those patients with temporal lobe lesions that displayed a unilateral decrease or suppression of audiospinal facilitation, the cortical lesion occupied the posterior part of the superior temporal gyrus (Heschl's gyrus) and a variably sized adjacent part of the planum temporale. This region corresponds to the auditory areas, as they have been described both anatomically and functionally in man (areas 41 and 42) (Brodmann, 1909; Celesia and Puletti, 1969; Galaburda and Sanides, 1980). This unilateral (contralateral) effect is surprising because of the bilateral projection of the auditory afferents. In fact, in auditory cortex (Harrison and Warr, 1962; van Noort, 1969) as well as in subcortical relays (Semple and Aitkin, 1979), the contralateral auditory input is represented more strongly than the ipsilateral one. In man, recordings in auditory cortex with depth electrodes or by magnetoencephalographic techniques confirm these results (Elberling *et al.*, 1982; Liegeois-Chauvel *et al.*, 1987).

This unilateral decrease in ASF by lesions of auditory areas could be interpreted either as a lack of facilitation or a reinforcement of physiological inhibition. This latter hypothesis may be advanced since the majority of the patients with lesions of the superior temporal gyrus had epilepsy, and thus presumably there were neurons in regions adjacent to the lesion whose hyperexcitability could have resulted in exacerbation of long-loop reflexes induced by auditory stimulation (Chauvel *et al.*, 1978). If an inhibitory control were exerted by the auditory cortex on subcortical nuclei, it should simply be increased by the paroxysmal activity. Two experimental arguments run counter to this hypothesis. (1) We have performed the same experiments in 4 subjects (Cases 1, 3, 4, 5) with an epileptogenic lesion including the superior temporal gyrus and no ASF before corticectomy. After corticectomy of the epileptogenic area and recovery from epilepsy, the ASF remained depressed. (2) We have studied 2 patients (Cases 11, 12) with a nonepileptogenic lesion of the superior temporal gyrus. We observed a similar decrease of ASF when the ear contralateral to the lesion was stimulated.

It is necessary to analyse how the auditory cortex can exert this facilitatory control. Most experimental studies performed in various preparations have linked the startle reaction with the activity of subcortical circuits (Forbes and Sherrington, 1914; Prosser and Hunter, 1936; Wright and Barnes, 1972; Hammond, 1973; Groves *et al.*, 1974; Davis *et al.*, 1982). Nonetheless, Buser *et al.* (1966) have demonstrated the facilitatory influence of the auditory cortex on the startle reflex in chloralose anaesthetized cats. In man, there are arguments in favour of auditory cortex participation, in addition to those provided by the present results. For example, in patients with bitemporal damage, including Heschl's gyrus, many authors have reported a lack of the startle response to unexpected sounds (Ho *et al.*, 1987; Mendez and Geehan, 1988). One possibility would be direct control exerted via a direct pathway from the auditory cortex to the inferior colliculus (Andersen *et al.*, 1980*a*, *b*).

An alternative possibility is that concurrent and indirect control is exerted through corticocortical connections. The primary auditory area (area 41) only sends projections to associative auditory area (area 42). In contrast, area 42 has many intra and interhemispheric projections (Bailey *et al.*, 1943; Bignall, 1969; Pandya *et al.*, 1969). The temporofrontal connections are dominant (Pandya and Kuypers, 1969) and the premotor area of the frontal lobe is well known to modulate the excitability of motoneurons either via direct connections with area 4 (Pandya and Vignolo, 1971), or via corticospinal pathways (Palmer *et al.*, 1980). In our patients, these temporofrontal projections might have been interrupted at their origin by posterior temporal lesions, which could explain the audiospinal dysfacilitation observed in those patients with temporal lobe lesions, as well as in the 3 patients with frontal lobe lesions, where the loop could have been interrupted at its second relay.

In summary, our data support the idea that ASF could involve a corticocortical pathway from primary and associative auditory area to frontal premotor and motor areas, but further studies are needed to elucidate its precise anatomical and functional substrates.

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APPENDIX

1. *Temporal lobe lesions*

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Neurological status**	*Type of clinical investigation*	*Anatomical lesion**
1. (P.E.N.)	F	34	Unknown	1. R T lobe seizures 2. Seizure free No deficit	CT scan STNR SEEG	1. Calcified lesion occupying the medial and caudal part of R Heschl's gyrus and the medial half of planum temporale (17 × 18 × 17 mm) 2. R T corticectomy including entire STG but excluding planum temporale
2 (P.A.S.)	M	24	Unknown	R T lobe seizures No deficit	CT scan STNR	Calcified lesion in the lat. and rostral part of R Heschl's gyrus (14 × 13 × 13 mm)
3 (G.E.F.)	M	21	Unknown	1. R T lobe seizures 2. Seizure free No deficit	CT scan STNR SEEG	1. Nontumoral cyst in the R T lobe white matter, middle part, at the level of MTG and ITG (lesioning fibres arising from and reaching STG, MTG, ITG (36 × 26 × 32 mm) 2. R T lobectomy
4 (L.A.R.)	M	27	Unknown	1. R T lobe seizures 2. Seizure free No deficit	CT scan STNR SEEG MRI	1. Dystrophic temporal lesion in the ant. part of R STG (33 × 30 × 29 mm) 2. R T corticectomy including MTL structures and LTL neocortex (MTG, ITG)
5 (G.E.N.)	M	15	Unknown	1. R T lobe seizures 2. Seizure free No deficit	CT scan STNR SEEG MRT	1. Calcified lesion in the posterior part of R STG including the rostrolat. portion of Heschl's gyrus (18 × 15 × 13 mm) 2. Ablation of entire R STG and MTG
6 (C.O.U.)	M	40	Unknown	L T lobe seizures No deficit	CT scan	Dilatation of body of lateral ventricle
7 (P.A.Q.)	F	30	Infantile encephalitis	L T lobe seizures No deficit	CT scan STNR	L temporal horn dilatation
8 (L.A.V.)	M	20	Unknown	L TP lobe seizures No deficit	CT scan STNR	Cystic noninfiltrating low grade glioma in mid. portion of L MTG (28 × 20 × 28 mm)
9 (K.O.J.)	M	25	Unknown	Seizure free No deficit	CT scan STNR SEEG	R MTL and total STG corticectomy
10 (H.E.R.)	M	26	Obstetric injury	L TP lobe seizures No deficit	CT scan	No apparent lesion
11 (B.U.H.)	M	23	Unknown	No seizure No deficit Headache	CT scan STNR MRI	Cortical dysplasic lesion in the mid. part of L Heschl's gyrus
12 (L.E.H.)	M	42	Cerebral haemorrhage	No seizure Headache	CT scan	Spheric anteriovenous angioma situated in the superior and caudal part of the RT lobe (1 cm)

2. Temporal lobe lesions outside Heschl's gyrus

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Neurological status**	*Type of clinical investigation*	*Anatomical lesion**
13 (D.E.T.)	M	26	Meningo encephalitis	R T lobe seizures No deficit	CT scan STNR SEEG	R cranial and cerebral atrophy predominantly affecting the body of the lateral ventricle
14 (E.D.E.)	F	32	Unknown	R T lobe seizures No deficit	CT scan STNR SEEG	No apparent lesion
15 (R.O.U.)	M	33	Unknown	Seizure free No deficit	CT scan STNR SEEG	R T lobe corticectomy sparing the posterior part of STG
16 (C.H.A.)	M	24	Unknown	Seizure free No deficit	CT scan STNR SEEG	R T lobe corticectomy sparing the posterior part of STG
17 (A.Z.E.)	M	25	Meningo-encephalitis	Seizure free No deficit	CT scan STNR SEEG	R T inferior parietal and periinsular corticectomy
18 (A.U.B.)	M	33	Oligodendro-glioma	Seizure free No deficit	CT scan STNR SEEG	L anterior temporal lobectomy sparing the posterior part of STG
19 (L.E.B.)	F	40	Unknown	Seizure free No deficit	CT scan STNR SEEG	L T corticectomy sparing STG
20 (C.O.L.)	M	35	Influenzal encephalitis	Seizure free Impairment of verbal fluency	CT scan STNR SEEG	L T corticectomy sparing STG
21 (D.O.U.)	M	15	Unknown	Seizure free	CT scan STNR SEEG	R T corticectomy sparing the posterior part of STG

3. Frontal lobe lesions

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Neurological status**	*Type of clinical investigation*	*Anatomical lesion**
27 (B.O.S.)	M	33	Post-traumatic	Seizure free Decrease of verbal fluency	CT scan STNR SEEG	R frontal corticectomy, medial and lateral, posteriorly limited by the precentral area
28 (K.A.L.)	F	29	Astrocytoma	Seizure free Slight spasticity R upper and lower limbs	CT scan STNR SEEG	L frontal corticectomy including superior frontal gyrus (lateral and medial), mid. frontal gyrus (superior part) and ant. cingulate gyrus
29 (D.E.S.)	M	24	Post-traumatic	Seizure free No deficit	CT scan STNR SEEG	R frontal corticectomy, medial and lateral, posteriorly limited by the precentral area
30 (T.H.Y.)	M	18	Low grade astrocytoma	Seizure free No deficit	CT scan STNR SEEG	R medial prefrontal and orbitofrontal corticectomy. R medial temporal resection (amygdala and hippocampus)
31 (M.O.U.)	M	21	Spont. intra-cerebral haematoma	Seizure free No deficit	CT scan STNR SEEG	R frontal corticectomy, medial and lateral, posteriorly limited by the precentral area
32 (G.E.L.)	M	22	Post-traumatic	L frontal lobe seizures	CT scan STNR SEEG	L prefrontal and medial frontal intermediary posttraumatic damage

4. *Occipital lobe lesions*

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Neurological status**	*Type of clinical investigation*	*Anatomical lesion**
22 (S.O.U.)	F	22	Perinatal hypoxia	L occipital seizures R hemianopia	CT scan STNR	L occipital horn dilatation. Parieto-occipital cyst
23 (G.A.L.)	F	17	Perinatal hypoxia	L hemianopia Seizure free	CT scan STNR SEEG	R lateral and medial occipital corticectomy
5. *Parietal lobe lesions*						
24 (T.R.O.)	F	14	Infantile encephalitis	R astereognosis R brachial weakness L parietal seizures	CT scan	L temporoparieto-occipital junction cortical atrophy
25 (F.R.A.)	M	17	Tumour	R parietal seizures No deficit	CT scan STNR SEEG	R inferior parietal low grade astrocytoma
26 (B.E.A.)	M	31	Unknown	R parietal seizures No deficit	CT scan	No apparent lesion

* Summary of neurological status and anatomical lesion topography at the time of neurophysiological investigations 1, before surgery; 2, after surgery.

MTG = medial temporal gyrus; MTL = medial temporal lobe; STG = superior temporal gyrus; ITG = inferior temporal gyrus; R = right; L = left; T = temporal; TP = temporoparietal; STNR = stereotactic neuroradiological investigations; SEEG = stereoelectroencephalographic exploration; MRI = magnetic resonance imaging.

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RECOVERY FROM ACUTE EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN THE LEWIS RAT

EARLY RESTORATION OF NERVE CONDUCTION AND REPAIR BY SCHWANN CELLS AND OLIGODENDROCYTES

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SUMMARY

Light and electron microscopic histological studies and electrophysiological studies were performed on Lewis rats with acute experimental allergic encephalomyelitis (EAE) induced by whole spinal cord or myelin basic protein to determine the mechanism of clinical recovery. In these animals, total clinical recovery from complete paraplegia may occur as early as 4 days after the onset of hindlimb weakness. These studies indicate that this recovery occurs at a time when there is restoration of nerve conduction in the peripheral nervous system (PNS) and central nervous system (CNS) and when most demyelinated fibres have been invested, and some partially remyelinated, by Schwann cells or oligodendrocytes in the PNS and CNS, respectively. These findings support the hypothesis that the neurological signs of acute EAE are due to demyelination in the PNS and CNS.

INTRODUCTION

Experimental allergic encephalomyelitis (EAE) is a disease of the nervous system induced by inoculation with whole central nervous tissue, purified myelin basic protein (MBP) or myelin proteolipid protein, together with adjuvants (Hashim *et al.*, 1980; Raine, 1984). It is widely studied as an animal model of human central nervous system (CNS) demyelinating disease, particularly multiple sclerosis (MS). EAE may have either an acute or a chronic relapsing course, but each form produces the same neurological signs, namely tail paralysis and limb ataxia, weakness and paralysis. Acute EAE is a monophasic disease like the human disease, acute disseminated encephalomyelitis, while chronic relapsing EAE has a relapsing remitting course resembling MS. In chronic relapsing EAE there are large plaques of CNS demyelination as in MS. However, in acute EAE such plaques are rare or do not occur. In fact, because of reports of the absence of demyelination in some animals with neurological signs of EAE it has been

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suggested that the neurological deficits of acute EAE and of the first episode of chronic relapsing EAE are due not to demyelination (Hoffman *et al.*, 1973; Lassmann and Wiśniewski, 1979; Panitch and Ciccone, 1981; Raine *et al.*, 1981; Simmons *et al.*, 1981, 1982; Kerlero de Rosbo *et al.*, 1985), but to other factors such as oedema (Paterson, 1976; Simmons *et al.*, 1982; Kerlero de Rosbo *et al.*, 1985; Sedgwick *et al.*, 1987) or an impairment of monoaminergic neurotransmission (Carnegie, 1971; White, 1984). It has also been suggested that neurological recovery from acute EAE is too rapid to be accounted for by remyelination, and therefore that demyelination cannot be the cause of the neurological signs (Panitch and Ciccone, 1981; Simmons *et al.*, 1981). However, these studies have either failed to use sensitive histological techniques to detect demyelination or have failed to examine the whole nervous system thoroughly, particularly the lumbar, sacral and coccygeal spinal cord and the peripheral nervous system (PNS), which is known to be involved in EAE. We have recently shown that demyelination in the PNS and the CNS is an important cause of the neurological signs in acute EAE by demonstrating demyelination and nerve conduction abnormalities in the dorsal root ganglia of rabbits (Pender and Sears, 1982, 1984) and, to a lesser extent, of rats with EAE induced by whole spinal cord (Pender and Sears, 1986), at the ventral root exit zone of the spinal cord in rats with EAE induced by whole spinal cord (Pender, 1986*a*, 1988*a*) and in the dorsal roots, ventral roots and ventral root exit zone in rats with EAE induced by MBP (Pender, 1986*b*, 1987, 1988*b*). Rats with hindlimb weakness due to EAE induced by whole spinal cord or MBP were found to have a reduced hindfoot H reflex which can be accounted for by demyelination affecting the CNS and PNS components of the monosynaptic reflex pathway (Pender, 1988*a*, *b*). In this report the rapid neurological recovery in rats with acute EAE induced by whole spinal cord or MBP is shown to be associated with the restoration of nerve conduction in the PNS and CNS at the time of investment and remyelination of demyelinated fibres by Schwann cells and oligodendrocytes.

MATERIAL AND METHODS

Animals

Male Lewis rats (JC strain) were kept 5 to a cage and with an unrestricted cage supply of rat and mouse cubes and water.

Induction of EAE

MBP-induced EAE. MBP was prepared from guinea pig spinal cord (after removal of the spinal roots) by the method of Deibler *et al.* (1972). MBP in 0.9% saline was emulsified in an equal volume of incomplete Freund's adjuvant (Commonwealth Serum Laboratories, Melbourne, Australia) containing 4 mg/ml of added Mycobacterium butyricum (Difco). Under ether anaesthesia rats, 8–10 wks old, were inoculated with 0.1 ml of emulsion in one footpad of each hindfoot. The total dose of MBP was 50 μg/rat.

Whole spinal cord-induced EAE. The inoculum was a homogenate of equal volumes of a 30% suspension of guinea pig spinal cord (the spinal roots having been removed) in 0.9% saline and a suspension of 4 mg of killed and dried Mycobacterium butyricum per ml of incomplete Freund's adjuvant. Rats, 8–10 wks old, received 0.05 ml of inoculum in the footpad of each of the four feet or 0.1 ml in one footpad of each hindfoot.

Management of inoculated animals

The rats were examined daily from the seventh day postinoculation and the clinical signs were recorded using the previously published grading system (Pender, 1986*b*). Hindlimb weakness was graded thus: 0 = no weakness; 1 = slight dragging of the toes of both hindfeet; 2 = severe dragging of both hindfeet but not of the rest of the hindlimbs; 3 = severe dragging of both hindlimbs, often with both hindlimbs displaced to one side of the body; 4 = total paralysis of the hindlimbs. Electrophysiological studies were performed in terminal experiments on 10 rats with MBP-induced EAE (5 at the peak of hindlimb weakness and 5 that had just fully recovered from hindlimb weakness) and on 12 rats with whole spinal cord-induced EAE (5 at the peak of hindlimb weakness and 7 after recovery from hindlimb weakness). Histological studies were carried out on 5 rats with MBP-induced EAE (3 at the peak of hindlimb weakness and 2 during or immediately after recovery from hindlimb weakness) and on 5 rats with whole spinal cord-induced EAE (4 at the peak of hindlimb weakness and 1 after recovery from hindlimb weakness). The last animal was studied electrophysiologically before it was perfused for histological study.

Controls

Normal male Lewis rats, 10–12 wks old, served as controls for the histological (2 rats) and electrophysiological studies (9 rats). As these studies were performed on the animals with EAE about 2 wks after inoculation, the control animals were the same age as the animals with EAE when studied.

Electrophysiological studies

Anaesthesia. Anaesthesia was induced with urethane (25% in 0.9% saline, intraperitoneal (i.p.), 5 ml/kg for controls, 4 ml/kg for rats with EAE undergoing H reflex studies but not laminectomy, and 4–5 ml/kg for rats with EAE undergoing laminectomy for ventral root and ventral root exit zone recordings). The dose of urethane/kg required to obtain a given depth of anaesthesia was lower in rats with EAE than in normal controls. Pentobarbitone sodium (i.p., 12 mg/kg) supplemented the urethane anaesthesia. The animals breathed spontaneously through a tracheostomy. At the beginning of each experiment 9 ml of Hartmann's solution (compound sodium lactate BP, Travenol) were given i.p.

M wave and H reflex recordings. The rat was mounted in an animal frame, and a metal box, through which water at 37° C was circulated, was placed under the animal. Because of the effects of anaesthetics on synaptic transmission it was important that, for the H reflex studies, an adequate depth of anaesthesia was maintained without depressing the corneal reflex. The left sciatic nerve was exposed in the posterior thigh and immersed in paraffin oil maintained at 37° C by radiant heat. Under these conditions the rectal temperature was 37° C–38° C. The freed sciatic nerve was lifted away from the volume conductor and stimulated in continuity with platinum electrodes 3 mm apart (cathode distal) delivering 0.1 ms square-wave voltage pulses at 1 Hz. Recordings were made with a 25 gauge needle electrode in the belly of the fourth dorsal interosseus muscle and with a reference 25 gauge needle electrode subcutaneously in the plantar aspect of the distal fourth digit of the left hindfoot.

Ventral root and ventral root exit zone recordings. Under urethane and pentobarbitone anaesthesia a T12–L4 laminectomy was performed and the left sciatic nerve was exposed in the posterior thigh as previously described (Pender and Sears, 1986). Radiant heat maintained the laminectomy and sciatic nerve pools at 37° C. The left L2–L6 dorsal roots were cut close to the spinal cord and displaced laterally. By freeing the two most caudal left denticulate ligaments from the dura and tying them to right paravertebral tendons, the spinal cord was rotated through 90° so that its ventral surface faced laterally to the left (*see* Pender, 1986*a*). The freed left sciatic nerve was lifted away from the volume conductor and stimulated in continuity with platinum electrodes 3 mm apart delivering 0.1 ms square-wave voltage pulses at 1.0 Hz. Volume conductor recordings were made with a 0.5 mm diameter silver ball electrode over one or more, in turn, of the left L4, L5 and L6 ventral roots (VRs), 1-3 mm distal to the respective ventral root exit zones (VREZs), and over the rostral parts of the VREZs. A reference electrode was placed on the right paravertebral region at the same level. At the end of each experiment the dissection was extended to confirm that the L4 and L5 spinal nerves always gave large contributions to the sciatic nerve and that the L3 and L6 spinal nerves gave small contributions.

Statistical analysis

Analysis of variance was used to compare the recordings from normal control rats with those from rats with hindlimb weakness due to MBP-induced EAE (Pender, 1988*b*), rats with hindlimb weakness due to whole spinal cord-induced EAE (Pender, 1988*a*) and rats recovering from each form of EAE to minimize the chance occurrence of statistically significant differences when multiple comparisons were made.

Histological studies

The methods have been described in detail previously (Pender, 1985, 1986*b*). Under ether anaesthesia the rats were perfused through the left ventricle with 0.9% saline followed by 2.5% (or 2%) glutaraldehyde/2% formaldehyde in 0.1 M sodium cacodylate buffer (pH 7.3-7.4). The brain, optic nerves, spinal cord, dorsal and ventral roots, dorsal root ganglia, spinal nerves, sciatic and tail nerves were removed and immersed in fixative. The tissues were postfixed with 2% osmium tetroxide and were embedded either in HistoResin (LKB Bromma) or Epok 812 (Ernest F. Fullam, Schenectady, NY). HistoResin sections (2 μm) were stained with toluidine blue in phosphate buffer (pH 7.6) or with cresyl violet. Semithin (1 μm) Epok 812 sections were stained with toluidine blue for light microscopy, and ultrathin sections were double-stained with uranyl acetate and lead citrate and examined in a Philips 301 electron microscope.

RESULTS

Clinical findings

Distal tail weakness commenced 8-11 days after inoculation and was followed by flaccid tail paralysis, hindlimb weakness and sometimes hindlimb paralysis. Forelimb weakness occurred occasionally. The temporal profiles of hindlimb weakness in rats undergoing H reflex studies are shown in fig. 1. This shows that hindlimb weakness commenced earlier and lasted longer in rats with whole spinal cord-induced EAE than in rats with MBP-induced EAE. For both whole spinal cord-induced EAE and MBP-induced EAE the time course and severity of maximal hindlimb weakness were similar for animals studied at the time of peak hindlimb weakness and for those studied after recovery from hindlimb weakness. The ascending tail weakness was accompanied by an ascending impairment of tail nociception as previously described (Pender, 1986*b*). The recovery process began rapidly. Often there was complete recovery of tail nociception and of hindlimb motor function by 15 days after inoculation, but moderate tail weakness persisted for several days longer. By 20 days after inoculation there was usually only mild distal tail weakness. The shortest time for total clinical hindlimb recovery from

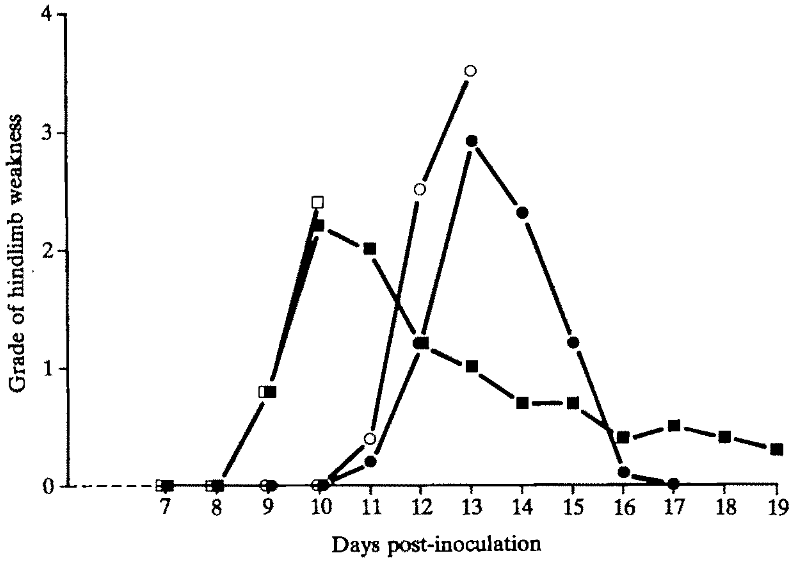


FIG. 1. Mean grades of hindlimb weakness plotted against days postinoculation in rats with whole spinal cord-induced EAE (squares) and rats with MBP-induced EAE (circles). The hindlimb weakness in the 5 animals undergoing H reflex studies at the peak of hindlimb weakness (open squares and circles) and in the 5 undergoing H reflex studies after recovery from hindlimb weakness (closed squares and circles) are shown for each type of EAE. If the grades differed between hindlimbs in the same animal, the mean of the two grades was used for that animal. The graphs show that hindlimb weakness commenced earlier and lasted longer in whole spinal cord-induced EAE than in MBP-induced EAE.

complete paraplegia was 4 days after the onset of hindlimb weakness, and this was in a rat with MBP-induced EAE.

H reflex studies

Normal controls

The results of studies on the fourth dorsal interosseus H reflex and M wave elicited by direct sciatic nerve stimulation in normal controls are shown in figs 2, 3 and 4 and the Table. The H reflex was maximal at a lower stimulus intensity than that giving the maximal M wave. As the stimulus intensity was increased above that giving the maximal H reflex, the amplitude of the H reflex declined as a result of collision, in the ventral root, between the orthodromic impulses of the H reflex and antidromic impulses evoked by direct activation of sciatic nerve motor fibres. As the amplitude of the H reflex was greater after a period of no stimulation for several seconds, the maximal H reflex was usually recorded as the response to the first stimulus after a 5 s period of no stimulation. Selective sectioning and stimulation of individual lumbar spinal roots established that the H reflex of the fourth dorsal interosseus muscle is mediated through the L5 dorsal and ventral roots and to a lesser extent the L6 ventral root. The maximal reflex response obtained by sciatic nerve stimulation had the same amplitude as that

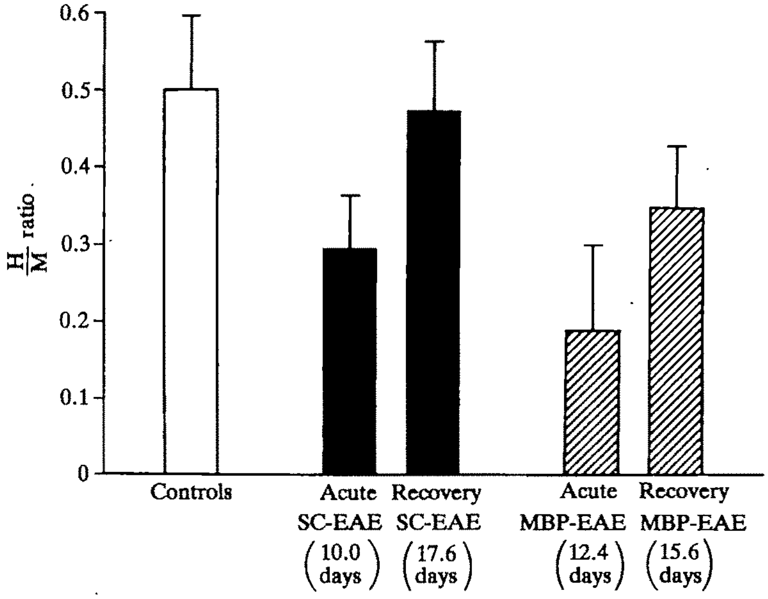
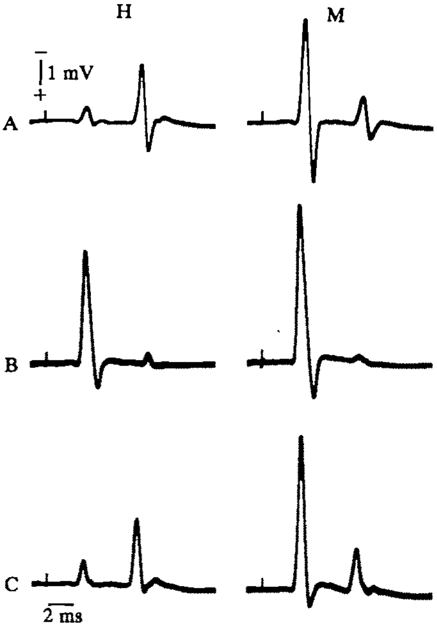


FIG. 2. Mean H/M ratios in normal control rats, rats at the peak of hindlimb weakness due to whole spinal cord-induced EAE (acute SC-EAE), rats after recovery from hindlimb weakness due to whole spinal cord-induced EAE (recovery SC-EAE), rats at the peak of hindlimb weakness due to MBP-induced EAE (acute MBP-EAE) and rats after recovery from hindlimb weakness due to MBP-induced EAE (recovery MBP-EAE). There were 5 rats in each group. Mean values are shown with 1 SD. The mean day (postinoculation) on which the studies were performed in each group is bracketed. There were highly significant differences between each of the following groups: acute SC-EAE and controls ($P < 0.005$); recovery SC-EAE and acute SC-EAE ($P < 0.005$); acute MBP-EAE and controls ($P < 0.001$); recovery MBP-EAE and acute MBP-EAE ($P = 0.01$).

elicited by selective L5 dorsal root stimulation, indicating that low intensity stimulation of the sciatic nerve did not result in significant collision in the ventral root. To assess the lumbar monosynaptic reflex pathway in EAE, direct sciatic nerve stimulation was used rather than L5 dorsal root stimulation because the former technique requires less anaesthesia (and hence less depression of synaptic transmission) and does not bypass the L5 dorsal root ganglion and distal dorsal root, which are sites of lesions in EAE. Under the controlled conditions used in these experiments the ratio of the peak-to-peak amplitude of the maximal H reflex to that of the maximal M wave (H/M ratio) has a narrow range in normal rats (fig. 2) and serves as a reliable indicator of the integrity of the monosynaptic reflex arc. It also allows the assessment of function in relation to a specifically defined muscle group.

MBP-induced EAE

In MBP-induced EAE the H/M ratio was severely reduced at the time of maximal hindlimb weakness and returned towards normal during recovery (fig. 2). At the peak of hindlimb weakness (12–13 days after inoculation), the M wave



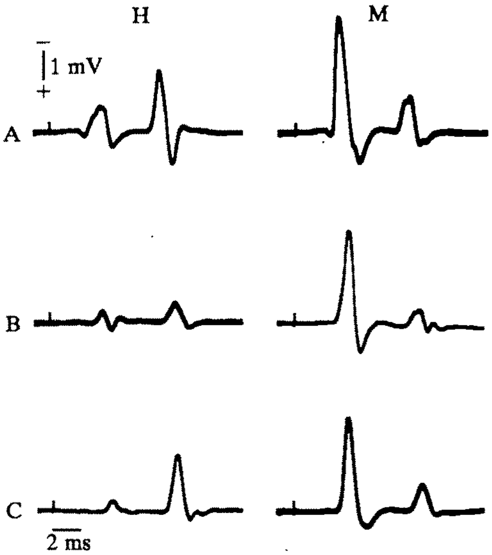


FIG. 3 (*left*). Maximal H reflex (H) and maximal M wave (M) elicited in the left fourth dorsal interosseus muscle by sciatic nerve stimulation in a normal control rat (A), in a rat on the day of onset of hindlimb weakness due to MBP-induced EAE (B) and in a rat on the first day of full clinical recovery from hindlimb weakness due to MBP-induced EAE (C).

FIG. 4 (*right*). Maximal H reflex (H) and maximal M wave (M) elicited in the left fourth dorsal interosseus muscle by sciatic nerve stimulation in a normal control rat (A), in a rat with hindlimb weakness due to whole spinal cord-induced EAE (B) and in a rat on the first day of full clinical recovery from hindlimb weakness due to whole spinal cord-induced EAE (C).

was normal but the H reflex was markedly reduced in amplitude, without temporal dispersion, and was of slightly prolonged latency (Pender, 1988*b*; fig. 3, Table). As shown in the Table there was a highly significant reduction in the mean H/M ratio compared with that in normal controls. These findings indicate normal conduction in peripheral nerve but interruption of the monosynaptic reflex arc. On the first day of complete clinical recovery of hindlimb motor function (15–17 days after inoculation) the mean H/M ratio was significantly greater than in animals with maximal hindlimb weakness but was still significantly less than in normal controls (figs 2, 3; Table). The interval between the onset of the M wave and the onset of the H reflex was shorter in rats after hindlimb recovery than in rats with maximal hindlimb weakness, but this difference was not statistically significant (Table).

Whole spinal cord-induced EAE

The findings in rats with whole spinal cord-induced EAE were similar to those described above. At the peak of hindlimb weakness (10 days after inoculation) the M wave was normal and the H reflex was reduced (Pender, 1988*a*; fig. 4, Table). As shown in fig. 2 and the Table there was a highly significant reduction

TABLE. M WAVES AND H REFLEXES IN EAE

Parameter	Controls	Groups (mean ± SD) $n = 5$ in each group				Analysis of variance	Comparisons between means					
		MBP-EAE		SC-EAE		Value and significance of F	Acute MBP-EAE and controls	Recovery MBP-EAE and controls	Recovery MBP-EAE and acute MBP-EAE	Acute SC-EAE and controls	Recovery SC-EAE and controls	Recovery SC-EAE and acute SC-EAE
		Acute	Recovery	Acute	Recovery							
M amp [a](mV)	4.6±1.1	5.7±1.3	5.9±1.4	4.6±1.6	3.2±1.2	$F = 3.19$ $P < 0.05$	n.s. ($P > 0.05$)	n.s.	n.s.	n.s.	n.s.	n.s.
$\frac{\text{H amp}}{\text{M amp}}$	0.50±0.09	0.19±0.11	0.35±0.08	0.29±0.07	0.47±0.09	$F = 10.44$ $P < 0.001$	$P < 0.001$	$P < 0.025$	$P = 0.01$	$P < 0.005$	n.s.	$P < 0.005$
M latency [b](ms)	2.23±0.34	2.42±0.24	2.30±0.15	2.39±0.28	2.52±0.33	$F = 0.84$ n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
M-H latency [c](ms)	4.62±0.28	5.12±0.52	4.84±0.34	4.87±0.26	4.68±0.33	$F = 1.49$ n.s.	$P < 0.05$	n.s.	n.s.	n.s.	n.s.	n.s.

Maximal M wave (M) and maximal H reflex (H) elicited in fourth dorsal interosseus muscle by sciatic nerve stimulation in normal control rats, rats with hindlimb weakness due to MBP-induced EAE (acute MBP-EAE), rats that have recovered from hindlimb weakness due to MBP-induced EAE (recovery MBP-EAE), rats with hindlimb weakness due to whole spinal cord-induced EAE (acute SC-EAE) and rats that have recovered from hindlimb weakness due to whole spinal cord-induced EAE (recovery SC-EAE).

[a] Peak-to-peak amplitude. [b] Latency to onset of maximal M wave. [c] Difference between latency to onset of maximal M wave and latency to onset of maximal H reflex.

n.s. = not significant.

in the mean H/M ratio compared with that in normal controls. After hindlimb recovery (14–25 days after inoculation) the mean H/M ratio was significantly higher than in rats at the peak of hindlimb weakness and was not significantly different from that in normal controls (figs 2, 4; Table). The H reflex was temporally dispersed in 1 rat showing recovery, although the latency to onset of the H reflex was not prolonged.

Ventral root and ventral root exit zone recordings

While the H reflex is a useful technique for studying nerve conduction in the entire lumbar monosynaptic reflex pathway, it has the disadvantage that it is also dependent on synaptic transmission. To assess nerve conduction directly, antidromically conducted compound action potentials evoked by sciatic nerve stimulation were recorded in the volume conductor over the lumbar VREZs and respective VRs in 2 rats showing hindlimb recovery (16 and 21 days after inoculation). In the normal control rat the VR response is a biphasic wave (positive, negative) with the negativity being greater than the initial positivity (figs 5A, 6A). The positivity is due to passive outward current driven by the approaching impulses, and the negativity is due to active inward current occurring during the rising phase of the action potential under the recording electrode. The VREZ response in the normal control rat is similar (figs 5A, 6A). In rats with hindlimb weakness due to whole spinal cord-induced EAE the VR recording is normal apart from a slight reduction in the conduction velocity of the peak negativity (Pender, 1988*a*). However, the VREZ recording shows a marked reduction in the

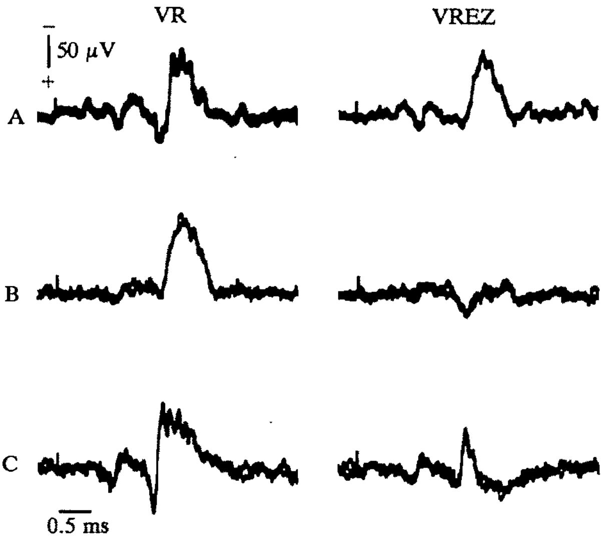


FIG. 5. Volume conductor recordings of the maximal L6 ventral root (VR) and L6 ventral root exit zone (VREZ) compound action potentials evoked by sciatic nerve stimulation in a normal control rat (A), in a rat with hindlimb weakness due to whole spinal cord-induced EAE (B) and in a rat 6 days after full clinical recovery from hindlimb weakness due to whole spinal cord-induced EAE (C).

amplitude of the negativity, indicating conduction block in many fibres at the VREZ (Pender, 1986*a*, 1988*a*; fig. 5B). In rats showing hindlimb recovery, the recordings over some lumbar VRs showed temporal dispersion due to slowing of conduction (fig. 6B). Such slowing probably indicates the restoration of conduction in previously blocked VR fibres, as was observed in the dorsal root ganglia of rabbits recovering from EAE (Pender and Sears, 1984). VREZ recordings in rats with hindlimb recovery revealed either a temporally dispersed waveform with a reduced negativity (fig. 6B) or a response with a negativity greater than the initial positivity (fig. 5C). The former is a complex waveform probably due to phase cancellations resulting from slowed conduction in the peripheral VR as well as slowed conduction through the VREZ; the latter indicates restoration of conduction in many fibres at the VREZ.

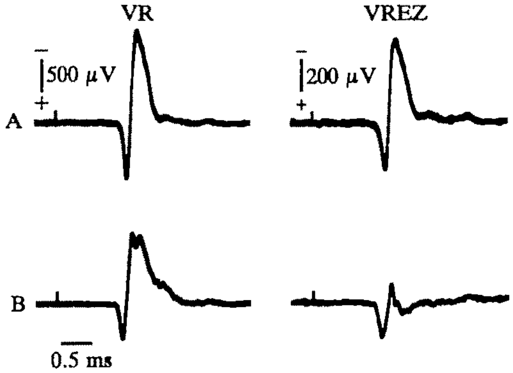


FIG. 6. Volume conductor recordings of the maximal L4 ventral root (VR) and L4 ventral root exit zone (VREZ) compound action potentials evoked by sciatic nerve stimulation in a normal control rat (A) and in a rat 6 days after full clinical recovery from hindlimb weakness due to whole spinal cord-induced EAE (B).

Histological findings

At the time of hindlimb weakness

In rats with hindlimb weakness due to whole spinal cord-induced EAE, there was perivascular and subpial inflammation and demyelination in the brainstem and spinal cord, and perivascular inflammation and demyelination in the dorsal root ganglia and dorsal and ventral spinal roots. There was minimal, if any, involvement of the spinal nerves and peripheral nerves. In the spinal cord the ventral root exit zones and the dorsal root entry zones were sites of predilection. The lesions in MBP-induced EAE were similar except that there was less demyelination in the spinal cord and minimal demyelination in the dorsal root ganglia (Pender, unpublished results). Electron microscopic examination showed invasion of the myelin sheath by macrophages containing myelin debris (fig. 7A) and association of demyelinated axons with such macrophages (fig. 7B). Some

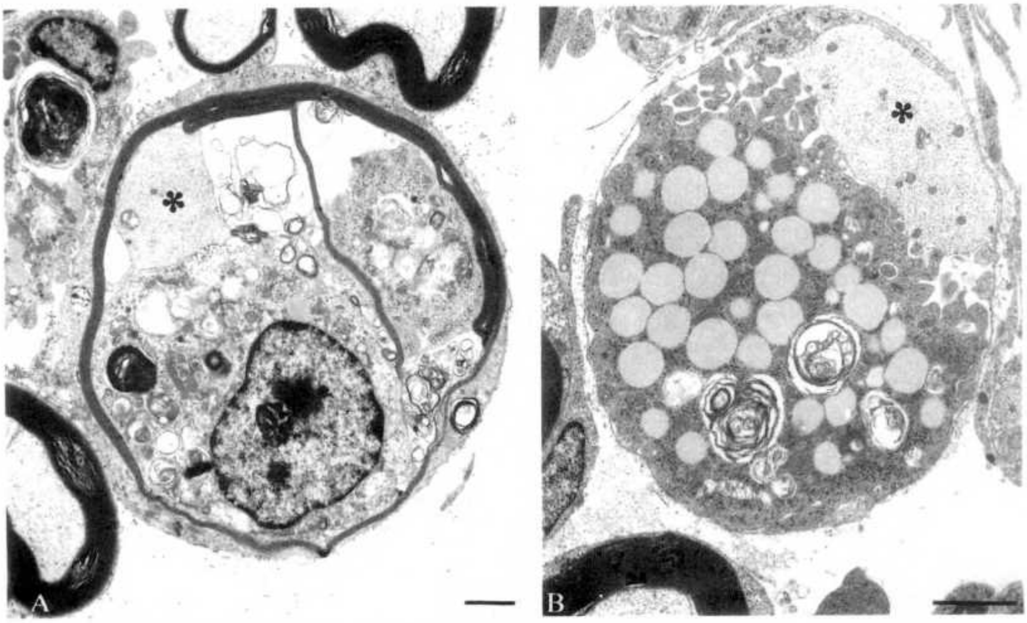


FIG. 7. Electron micrographs from a rat 2 days after the onset of tail weakness due to MBP-induced EAE (12 days after inoculation). A, first coccygeal dorsal root showing invasion of a myelin sheath by a macrophage containing myelin debris. The axon is shrunken (asterisk). B, S3 dorsal root showing a demyelinated axon (asterisk) closely associated with a macrophage containing myelin debris. Bars = 2 μm.

demyelinated PNS axons were invested by debris-free Schwann cell processes as described below during the recovery phase; however, only a small proportion of the invested fibres, and these were all small diameter fibres, showed any significant promyelin stage, and there was no evidence of compact myelin formation. Several degenerating fibres were seen.

During/after recovery from hindlimb weakness due to MBP-induced EAE

To investigate the structural basis of functional recovery, it was essential to examine tissue during early recovery. Here the detailed histology in rats during, or immediately after, recovery from hindlimb weakness due to MBP-induced EAE (15 days after inoculation) is described. The reparative processes detailed below occurred in lumbar, sacral and coccygeal segments.

PNS. Light microscopic examination of the PNS showed demyelinated axons (fig. 8A), axons with inappropriately thin myelin sheaths, and some degenerating axons. Electron microscopic examination of the PNS showed that the majority of demyelinated axons were invested by at least one, and often several, layer(s) of debris-free Schwann cell processes (figs 8B, 9) or by thin compact myelin within a Schwann cell basal lamina (fig. 10). The maximum number of myelin lamellae was 8. That these lamellae were the product of new myelin formation and not the

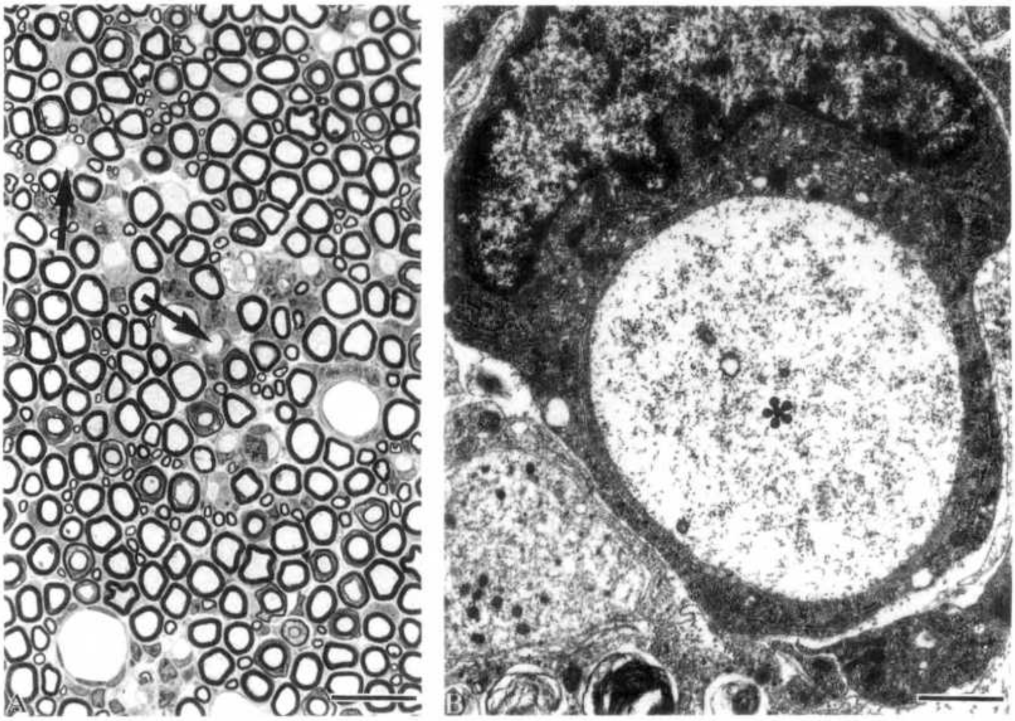


FIG. 8. A, transverse section through L5 ventral root of a rat recovering from complete paraplegia due to MBP-induced EAE, 15 days after inoculation. At this stage there was only mild hindlimb weakness. Demyelinated axons are present (arrows). Epok 812 section stained with toluidine blue. Bar = 25 μm. B, electron micrograph of L6 ventral root from the same animal showing investment of a demyelinated axon (asterisk) by a debris-free Schwann cell. Bar = 0.5 μm.

residue of partial demyelination was indicated by the criteria of Harrison *et al.* (1972) for remyelination. First, the configuration of the myelin resembled that seen during primary myelination in development. Secondly, unlike partially demyelinated fibres, the myelin lamellae were intact and were not invaded by debris-containing macrophages. Thirdly, thinly myelinated fibres with these characteristics of remyelination were seen only after a stage when completely demyelinated fibres were consistently found.

Occasionally there was dense undercoating of a region of demyelinated axolemma separated by a uniform intercellular cleft from a debris-free Schwann cell process loaded with mitochondria (fig. 11), suggesting the development of a new node-like axonal specialization, as described in amyelinated PNS fibres in the dystrophic mouse (Rosenbluth, 1979). In transverse sections such axonal specializations were restricted to short lengths of the circumference. In fig. 11 a node-like axolemmal specialization lies immediately adjacent to a region of exceedingly close apposition between the axolemma and the indenting Schwann cell process, a region reminiscent of the paranodal-type axolemmal specializations described in the same model

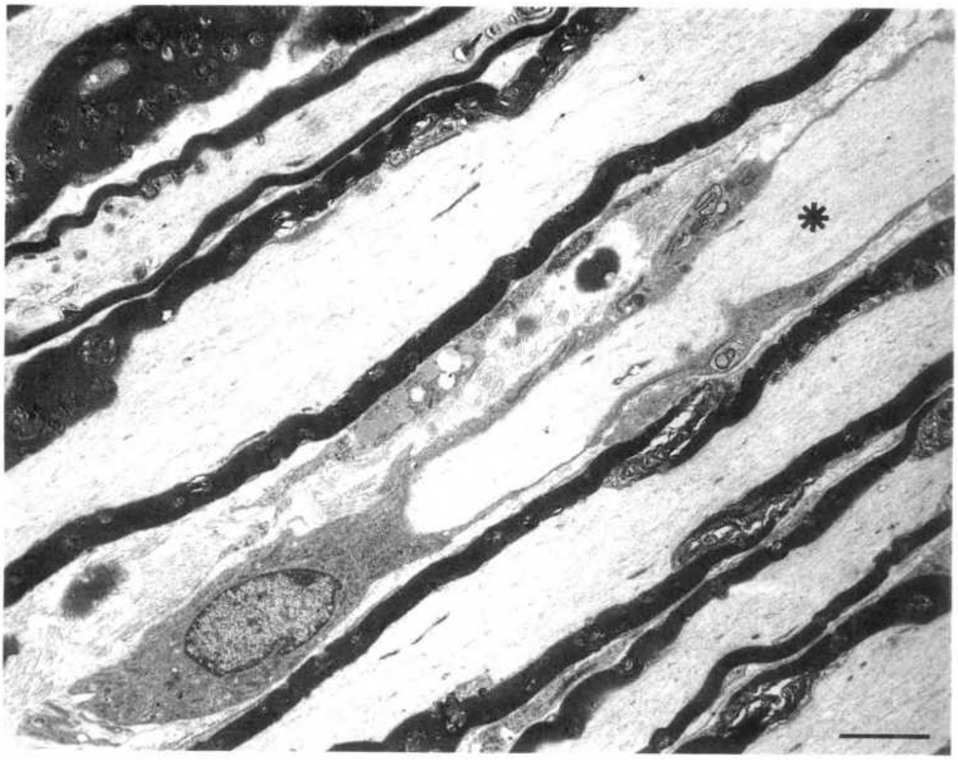


FIG. 9. Electron micrograph of S4 dorsal root of a rat that had just fully recovered from tail nociceptive impairment and hindlimb weakness due to MBP-induced EAE, 15 days after inoculation. A demyelinated axon (asterisk) is invested by a Schwann cell. Bar = 5 μm.

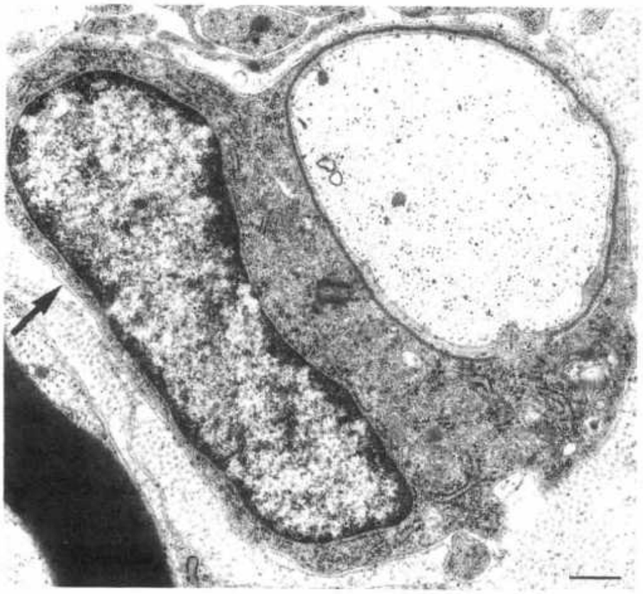


FIG. 10. Electron micrograph showing remyelination by a Schwann cell in the first coccygeal dorsal root of the same rat as in fig. 9. The basal lamina of the Schwann cell is visible (arrow). Bar = 0.5 μm.

(Rosenbluth, 1979). Macrophages containing myelin debris were also present in these lesions but, unlike the earlier lesions, their processes were separated from the demyelinated axons by debris-free Schwann cell processes, or new compact myelin, and a Schwann cell basal lamina.

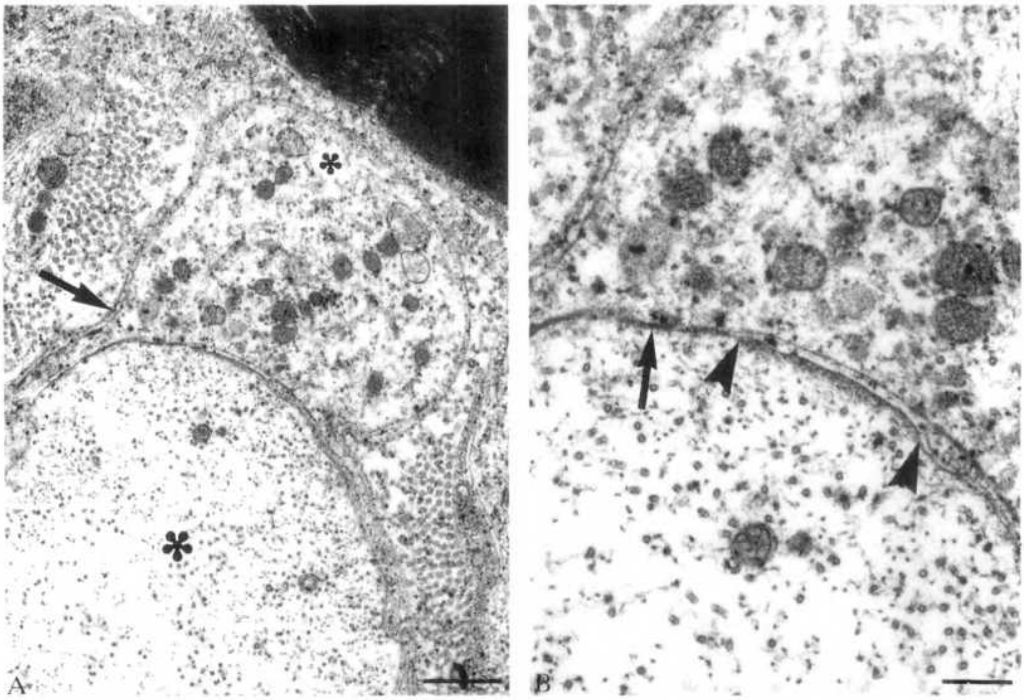


FIG. 11. Electron micrographs of L4 ventral root of a rat on the first day of full recovery from hindlimb weakness due to MBP-induced EAE, 15 days after inoculation. A, a demyelinated axon (large asterisk) is closely associated with a mitochondria-laden Schwann cell process (small asterisk) within a basal lamina (arrow). Bar = 0.5 μm. B, detail at higher power showing a region of subaxolemmal density (between arrowheads) where the axon is separated from the Schwann cell process by a relatively constant intercellular cleft. Adjacent to this region, the Schwann cell process is exceedingly closely apposed to the axolemma and indents it (arrow). Bar = 0.2 μm.

CNS. Light microscopic examination of the CNS showed demyelinated axons, some degenerating axons and resolution of inflammation in the spinal cord. Electron microscopic examination of the spinal cord showed demyelinated axons invested by debris-free glial processes without a basal lamina. It was sometimes difficult to distinguish between astrocyte and oligodendrocyte processes but at other times it was clear that demyelinated axons were invested by oligodendrocyte processes that could be distinguished from astrocyte processes by their denser cytoplasm and absence of intermediate filaments (fig. 12). Noninvested parts of the axolemma of oligodendrocyte-invested axons were often closely apposed to normally myelinated fibres (fig. 12). Occasionally there was compaction of an

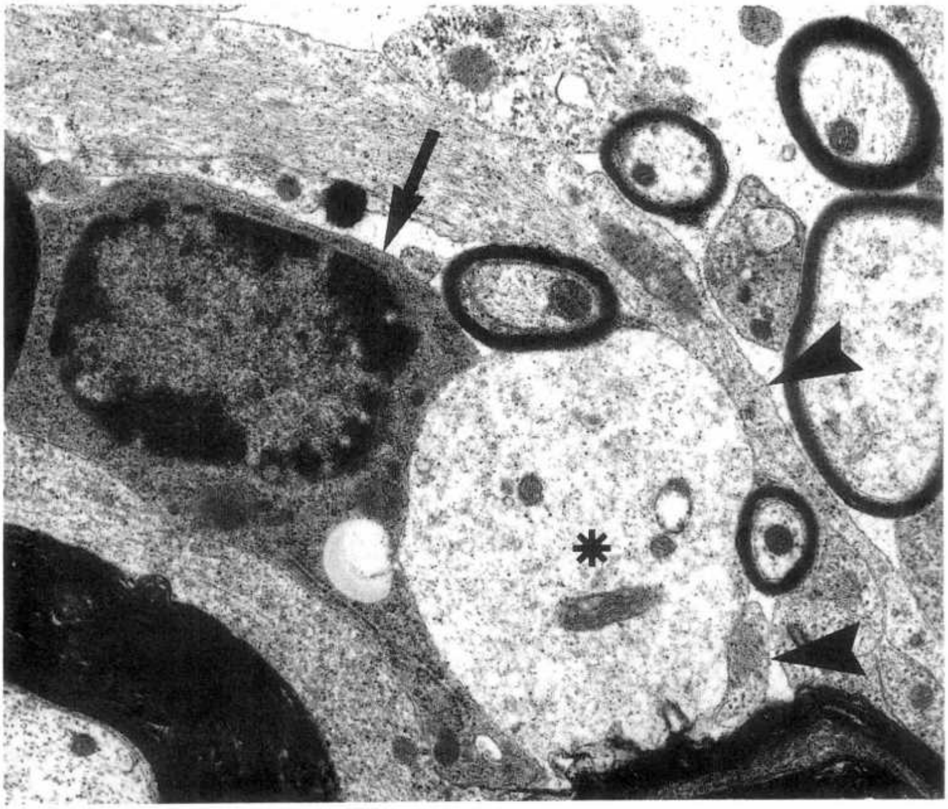


FIG. 12. Electron micrograph of a ventral column of the L5 spinal cord of a rat that had just fully recovered from hindlimb weakness due to MBP-induced EAE, 15 days after inoculation. A demyelinated axon (asterisk) is closely associated with an oligodendrocyte (arrow) and astrocytic processes (arrowheads). The demyelinated axolemma is also closely apposed to the outermost myelin lamellae of normally myelinated axons. Bar = 0.5 μm.

investing oligodendrocytic loop to form a major dense line. In the central tissue projection of the ventral root, an area normally myelinated by oligodendrocytes (Fraher and Kaar, 1986), there were demyelinated fibres invested by debris-free oligodendrocyte and astrocyte processes. Several of these fibres each had a region of subaxolemmal density in close association with an astrocytic process the membrane of which was separated from the axolemma by a uniform cleft. These regions were restricted to short lengths of the axonal circumference and closely resembled the node-like axolemmal specializations described in spinal cord demyelinated by ethidium bromide (Rosenbluth *et al.*, 1985). Some of these specializations lay immediately adjacent to paranodal-type axolemmal specializations closely associated with oligodendrocyte processes (*see* Rosenbluth *et al.*, 1985). The oligodendrocyte-invested fibres in the central tissue projection lay within a dense matrix of astrocyte processes enclosed within the glia limitans.

Around some axons the investing oligodendroglial loop was compacted to form a single myelin lamella. There was no evidence of investment or remyelination of CNS axons by Schwann cells, either in the spinal cord or in the central tissue projection.

After recovery from hindlimb weakness due to whole spinal cord-induced EAE

The following observations were made just after recovery from hindlimb weakness due to whole spinal cord-induced EAE (17 days after inoculation). The reparative processes described below were present in lumbar, sacral and coccygeal segments.

PNS. Light microscopic examination of the PNS showed demyelinated fibres, fibres with inappropriately thin myelin, and degenerating fibres in the dorsal root ganglia and spinal roots (fig. 13A). Electron microscopy of the PNS revealed Schwann cell investment and remyelination of demyelinated fibres as in the recovery phase of MBP-induced EAE, except that remyelination was generally

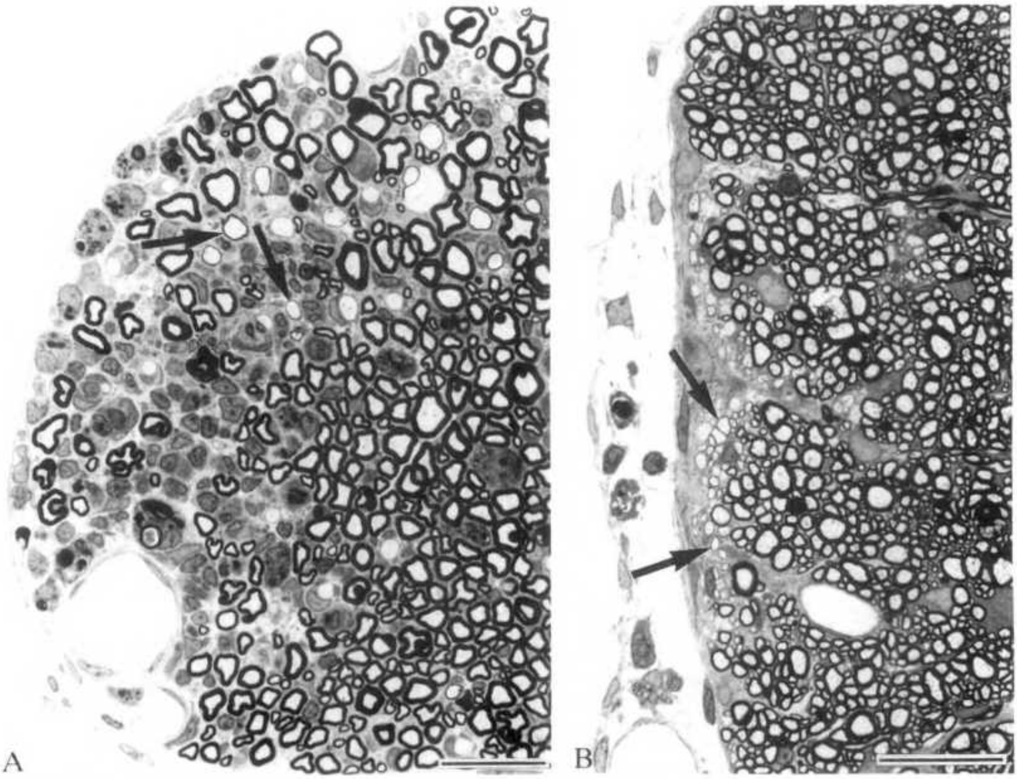


FIG. 13. A, transverse section through L6 ventral root of a rat that had just fully recovered from hindlimb weakness due to whole spinal cord-induced EAE, 17 days after inoculation. There is well established remyelination of many axons (arrows). B, transverse section through a ventral column of S4 spinal cord of the same animal. Many subpial axons (arrows) are being remyelinated. Epok 812 sections stained with toluidine blue. Bars = 25 μm.

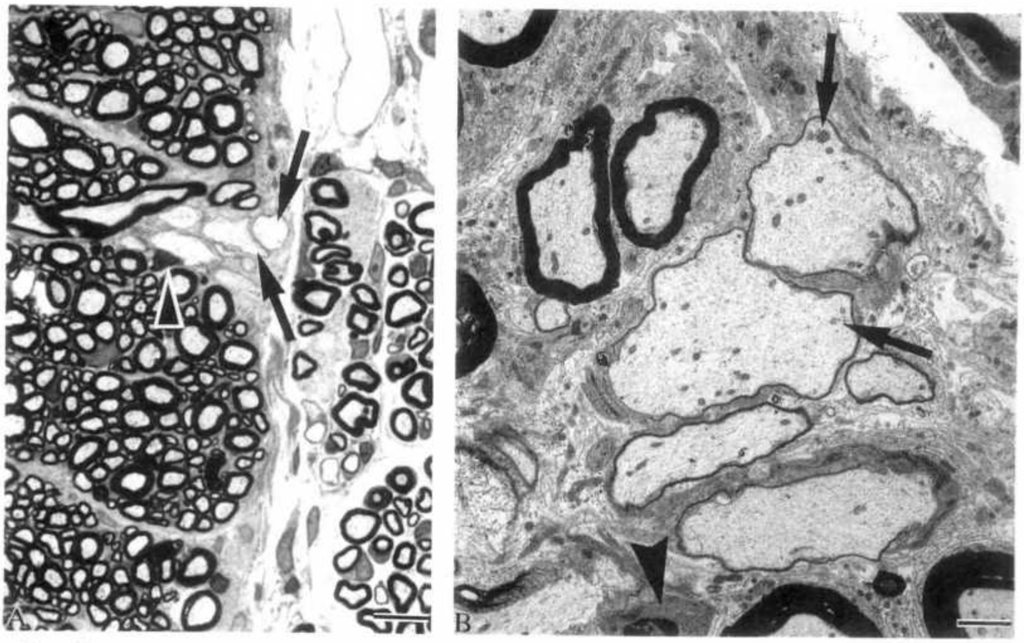


FIG. 14. A, transverse section through L5 ventral root exit zone of the spinal cord of the same rat as in fig. 13. Several fibres (arrows) in the CNS portion of the ventral root exit zone are being remyelinated. An oligodendrocyte (arrowhead) lies adjacent to one of these fibres. Epok 812 section stained with toluidine blue. Bar = 10 μm. B, electron micrograph showing detail in A. The same remyelinated fibres (arrows) and oligodendrocyte (arrowhead) can be seen. Bar = 2 μm.

more advanced, with the formation of up to 20 new myelin lamellae. The latter was probably because this study was made 2 days later than for MBP-induced EAE.

CNS. Light microscopic examination of the CNS showed demyelinated fibres, fibres with inappropriately thin myelin, and degenerating fibres in the spinal cord, and resolution of meningeal and spinal cord inflammation (figs 13B, 14A). The changes were similar to those in the recovery phase of MBP-induced EAE with the exception that there was more widespread remyelination because whole spinal cord-induced acute EAE results in more spinal cord demyelination (Pender, unpublished results). Electron microscopy of the spinal cord showed that there were many fibres being remyelinated with up to 7 new myelin lamellae. Such remyelinated fibres were found in the VREZ of the lumbar spinal cord (fig. 14B), in other subpial regions of the spinal cord (fig. 15) and in the central tissue projections of the ventral roots. The newly formed myelin sheaths in the VREZ were much thinner than the thin sheaths that occur here in normal rats (Pender, 1988*a*) and thus could be distinguished from the latter. It was concluded that the remyelination of the CNS was performed by oligodendrocytes rather than by Schwann cells because: (1) the newly formed myelin was not encircled by the

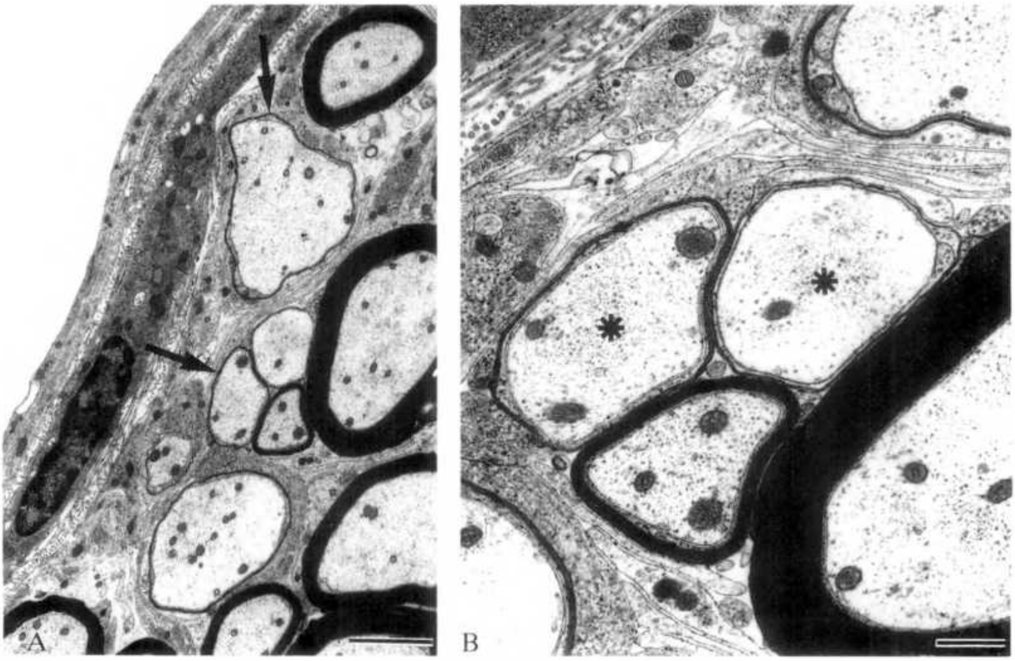


FIG. 15. A, electron micrograph showing remyelination of subpial axons (arrows) in a ventral column of L5 spinal cord of the same animal as in fig. 13. Bar = 2 μm. B, high power detail of A showing apposition of newly formed myelin sheaths of 2 axons (asterisks) without an intervening basal lamina. Bar = 0.5 μm.

cytoplasm of the myelinating cell but originated by the compaction of microtubule-laden cytoplasmic loops which occupied only a small proportion of the fibre circumference; (2) there was no basal lamina around any of the remyelinated fibres; and (3) the remyelinated fibres were closely apposed to each other and to normal myelinated fibres as in the normal CNS (fig. 15B). There was no evidence of investment or remyelination of CNS axons by Schwann cells, even within the transitional VREZ. Most of the CNS fibres that were still demyelinated were invested by debris-free oligodendrocyte and astrocyte processes. As in the recovery phase of MBP-induced EAE there were some demyelinated axons invested by glial cells with node-like and paranodal-type axolemmal specializations.

DISCUSSION

The present study demonstrates that, in acute EAE in the rat, rapid clinical recovery from hindlimb weakness is closely associated with the restoration of the hindfoot H reflex. The reduction in the amplitude, without temporal dispersion, of the H reflex in rats with hindlimb weakness due to EAE indicates either (1) conduction block in fibres mediating the reflex or (2) decreased synaptic transmission between the Ia afferent terminals and motor neurons. Demyelination and consequent conduction block in the L5 dorsal root ganglion, dorsal root, and dorsal root entry zone and L5 and L6 intramedullary ventral roots, ventral root exit zones (CNS and PNS) and extramedullary ventral roots can account for the depressed H reflex (Pender, 1988*a*, *b*). The lack of a major delay in the M-H latency could be accounted for by sparing of some of the fastest fibres. Demyelination of descending pathways in the brainstem and spinal cord could also alter the H reflex by increasing or decreasing excitability of the motor neuron pool. This may occur in whole spinal cord-induced EAE but seems unlikely in MBP-EAE, because of the paucity of CNS demyelination in the latter. The restoration of the H reflex during recovery is interpreted as indicating restoration of nerve conduction in CNS and PNS fibres mediating this reflex. This conclusion is supported by the temporal dispersion of the H reflex and the direct evidence of restoration of conduction in the ventral root and VREZ during recovery from whole spinal cord-induced EAE.

The recovery from hindlimb weakness and the restoration of the H reflex occur at a time when there is investment and remyelination of lumbar CNS and PNS axons by oligodendrocytes and Schwann cells, respectively. In the animals studied immediately after clinical hindlimb recovery there were considerably more demyelinated fibres invested by glial or Schwann cells than there were fibres with newly formed myelin. This suggests that conduction had been restored in fibres that were still demyelinated but which had been invested by debris-free glial or Schwann cells. Studies in noninflammatory models of PNS demyelination have shown that nerve conduction can be restored by the development of electrical excitability in demyelinated internodal axolemma as early as 4 days after the induction of demyelination (Bostock and Sears, 1978; Smith *et al.*, 1982). In the lysophosphatidyl choline model, restoration of conduction occurred when demyelinated fibres became closely associated with debris-free Schwann cells (Smith and Hall, 1980; Smith *et al.*, 1982), as was observed in the present study.

During recovery from EAE, areas of subaxolemmal density were occasionally observed in demyelinated axons in close association with astrocytic or mitochondria-laden Schwann cell processes. Such axolemmal specializations resemble the node-like specializations observed in regions of CNS demyelination induced by chronic EAE (Raine, 1978), cuprizone (Ludwin, 1980) and ethidium bromide (Blakemore and Smith, 1983; Rosenbluth *et al.*, 1985) and in amyelinated PNS fibres in the dystrophic mouse (Rosenbluth, 1979). It is possible that these subaxolemmal densities in rats recovering from acute EAE might be the morphological equivalents of the foci of inward current, termed 'phi nodes', found in ventral root axons demyelinated by lysophosphatidyl choline (Smith *et al.*, 1982). A recent ultrastructural study of the spinal cords of rats and guinea pigs with acute EAE found no evidence for the development of phi nodes, but this study was performed in animals with hindlimb paralysis and not during recovery (Black *et al.*, 1987). Thus the development of electrical excitability in CNS and PNS demyelinated fibres invested by glial or Schwann cells may be the mechanism for the rapid clinical recovery in acute EAE. Remyelination by oligodendrocytes and Schwann cells occurs rapidly and would make the restoration of conduction more secure (*see* Smith *et al.*, 1981).

The present findings support the hypothesis that demyelination of the PNS and CNS is the cause of the neurological signs of acute EAE induced by inoculation with either whole spinal cord or MBP (*see* Pender, 1987). Restoration of conduction in the ventral roots and VREZs would contribute to the recovery from hindlimb and tail paralysis while restoration of conduction in the sacrococcygeal dorsal root ganglia, dorsal roots and dorsal root entry zones would explain the recovery of tail nociception. The possibility that lesions of descending brainstem and spinal cord pathways with subsequent recovery might contribute to the development and resolution of hindlimb weakness was not investigated. Pender and Sears (1984) presented evidence for the restoration of conduction by the development of electrical excitability in demyelinated axons of the dorsal root ganglia of rabbits recovering from acute EAE but electron microscope studies were not performed. In contrast to the good correlation between clinical recovery and glial/Schwann cell ensheathment-remyelination in the present study, there is a poor correlation between neurotransmitter system changes and the clinical course of chronic relapsing EAE in the Lewis rat (Krenger *et al.*, 1986). The latter indicates that neurotransmitter system changes are not responsible for the temporary neurological signs, although axonal degeneration of monoaminergic neurons could of course contribute to persistent neurological deficits.

Previous studies have shown that remyelination occurs in the CNS and PNS of rats, rabbits and guinea pigs with EAE (Luse and McDougal, 1960; Bubis and Luse, 1964; Lampert, 1965; Prineas *et al.*, 1969; Raine *et al.*, 1969; Snyder *et al.*, 1975; Madrid and Wiśniewski, 1978; Lassmann *et al.*, 1980, 1986), in the CNS of mice with EAE (Brown *et al.*, 1982; Raine *et al.*, 1984) and in the PNS in experimental allergic neuritis (Ballin and Thomas, 1969). However, no previous study has defined the morphological changes associated with early recovery in EAE. In the present study, remyelination of the PNS was seen as early as 5 days after the onset of tail weakness, and remyelination of the CNS by oligodendrocytes was well advanced 9 days after the onset of tail weakness and possibly commenced as early as 6 days. Remyelination of CNS axons by Schwann cells has been observed in chronic EAE in the guinea pig (Snyder *et al.*, 1975; Lassmann *et al.*, 1980), mouse (Brown *et al.*, 1982; Raine *et al.*, 1984) and rat (Lassmann *et al.*, 1980). In the present study, demyelinated CNS axons were rapidly invested and remyelinated by oligodendrocytes and there was no evidence of investment or remyelination of CNS axons by Schwann cells. This suggests that Schwann cells myelinate CNS axons only when there is active inhibition of oligodendrocyte-mediated remyelination.

This rapid remyelination by oligodendrocytes in acute EAE is of particular interest in view of the recently reported evidence of early massive remyelination in MS (Lassmann, 1983; Prineas *et al.*, 1984). Glial ensheathment and remyelination may account for the rapid as well as the delayed recovery after relapses of MS. The rapidity of the recovery process described in the present study also has another important implication. The development of neurological signs in EAE and MS is likely to be determined not only by the degree but also by the time course of demyelination. Thus slowly evolving asynchronous demyelination may be less likely to cause dysfunction than rapid simultaneous demyelination in the same number of fibres. Therefore the clinical states of neurological deterioration, stability or recovery reflect a dynamic process in which active demyelination predominates over, equals or is dominated by these recovery processes.

In conclusion, the present study indicates that clinical recovery from acute EAE is due to rapid investment and remyelination of demyelinated PNS and CNS fibres by Schwann cells and oligodendrocytes. Thus the mechanisms for production of, and recovery from, the neurological signs in acute EAE may be the same as in relapses of chronic EAE. This emphasizes the fact that knowledge of the pathogenesis and pathophysiology of acute EAE is essential for viewing the processes of chronic relapsing EAE in perspective.

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THE EFFECTS OF VOLUNTARY CONTRACTION ON THE H REFLEX OF HUMAN LIMB MUSCLES

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SUMMARY

The effects of a voluntary contraction on the H reflexes of various muscles were quantified to determine whether the reflex responses were sufficiently reproducible to be used in diagnostic studies. During a voluntary contraction, H reflexes could be recorded reliably from tibialis anterior and abductor pollicis brevis, but accurate identification of the onset of the H wave from the on-going background EMG required duplicate averages of multiple responses. During a contraction the H reflex could be obtained at lower stimulus intensities in the forearm flexor muscles than when relaxed, and a more clear separation of the H wave from the M wave was possible. The background contraction abolished the attenuation of reflex amplitude with increasing stimulus repetition rates, such that repetition rates of up to 4 Hz could be used without significant loss of reflex amplitude. There were only small and usually insignificant differences in the latency of the H reflex or its variability when elicited with the forearm muscles relaxed and when flexor carpi radialis was contracting steadily.

The reflex latencies of abductor pollicis brevis, tibialis anterior and soleus were compared with F wave latencies for these muscles. The minimal F wave latencies were shorter than the H reflex latencies for abductor pollicis brevis (mean 2.2 ms) and tibialis anterior (mean 1.0 ms) but not for soleus. Comparison of the spread of F wave latencies (F max–F min) suggests that, for soleus, F waves are recorded only from the faster conducting motor units in the pool, presumably those less readily recruited in the H reflex. It was calculated that the distribution of motor conduction velocities responsible for the F waves of abductor pollicis brevis was 8.8 $\mathrm{m \cdot s^{-1}}$. This value underestimates the likely distribution of motor conduction velocities for the thenar muscle by as much as 50%, consistent with the view that F waves rarely occur in slowly conducting motor units, the units of lowest threshold in reflex studies. It is concluded that, for many motoneuron pools, the H reflex and the F wave appear preferentially in different motoneurons, low and high threshold, respectively, and that reflex studies can provide information not available from somatosensory evoked potentials or F wave studies.

INTRODUCTION

Routine neurological examination is dependent on the cooperation of the patient, whether it involves higher cortical function, reporting the perception of sensory

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stimuli, the maintenance of posture and balance, the performance of skilled movements or the exertion of maximal power. Reflex function is relatively immune to the vagaries of the patient's mental state and, not surprisingly, the elicitation of tendon reflexes and exteroceptive reflexes, such as the blink reflex and the plantar response, has become an indispensable part of routine examination. It is perhaps paradoxical that tests of spinal reflex function have not achieved the same preeminence as objective tests in neurophysiological studies.

There are three reasons why testing spinal reflex function has not received widespread acceptance. First, it is generally believed that the electrically elicited spinal proprioceptive reflex (the H reflex) can be recorded easily only from triceps surae. Secondly, the latency of the H reflex response is variable in different trials in the one subject and in comparisons between subjects. This results in a relatively wide normal range, particularly in comparison with other measures of nerve conduction. Thirdly, the electrical stimuli for the H reflex must be given at low rates because the response is attenuated significantly when the rate exceeds once every 5 s, a phenomenon termed 'low-frequency depression' (Ishikawa *et al.*, 1966; Cook, 1968; Hugon, 1973; Van Boxtel, 1986; Burke, 1987).

At least in theory, these three problems would be minimized if the electrical stimuli were delivered while the subject maintained a steady isometric contraction of the test muscle. A voluntary contraction of the test muscle is one of the best methods of reflex reinforcement, better even than the Jendrassik manoeuvre (Wartenberg, 1953). During a voluntary contraction, spinal proprioceptive reflexes can be recorded in virtually all accessible limb muscles (Hagbarth, 1962; Burke, 1987; *see also* Upton *et al.*, 1971; Iles, 1977; Eisen *et al.*, 1984*b*). The mere act of raising the motoneuron pool close to firing threshold should decrease the variability in latency due to the subthreshold component of the compound excitatory postsynaptic potential (EPSP). The rise-times of the compound EPSP responsible for spinal proprioceptive reflexes are long: > 10 ms for the ankle jerk and up to 5 ms for the H reflex of soleus (Burke *et al.*, 1983, 1984). With relaxed muscles, much of the compound EPSP is dissipated in raising the excitability of the motoneuron pool to firing threshold (Burke *et al.*, 1984), such that differences in the ability of subjects to relax can result in differences in reflex latency. By 'clamping' motoneuron excitability at a standard level, a voluntary contraction should eliminate this component of latency variability. In addition, it has been established that a voluntary contraction diminishes the dependence of H reflex amplitude on stimulus repetition rate for rates up to 1/s (Tóth *et al.*, 1979; Hoehler *et al.*, 1981; Rothwell *et al.*, 1986). However, even a rate of 1/s could involve the patient in maintaining a steady contraction for 4 min or longer if duplicate averages of small responses are to be undertaken to define the reflex latency accurately. Higher stimulus rates have been used by some authors (Eisen *et al.*, 1984*a*, *b*; Weiss and White, 1986) but there has been no formal documentation of the trade-off between stimulus rate and the latency and amplitude of the reflex potential.

The present study was undertaken to quantify the effects of a voluntary contraction on the H reflex of muscles of the upper and lower limbs, and to compare these data with F wave studies performed on the same muscles. The prime aim was to validate reflex studies during voluntary activity as a diagnostic tool, and to compare the information obtained from these studies with that provided by F wave studies.

METHODS

Repeated experiments were performed on 10 neurologically normal adult volunteers, each of whom gave informed consent to the procedures. The subjects ranged in age from 21 to 43 yrs and in height from 157 to 195 cm. When studies were performed on triceps surae the subjects lay on one side so that access could be obtained to the popliteal fossa. For other muscles, they reclined supine on a comfortable couch.

H reflexes were recorded at rest from the median-innervated forearm flexor muscles (flexor carpi radialis) and from soleus and, during voluntary activity of the test muscle, from flexor carpi radialis, abductor pollicis brevis and tibialis anterior. The evoked electromyogram (EMG) was recorded using surface electrodes up to 5 cm apart with the active electrode over the motor point of the relevant muscle. Subjects were given auditory feedback of the EMG to help maintain a steady voluntary contraction of the test muscle. In initial experiments, a Medelec Constant Tension Unit was used to ensure a steady contraction in studies of different contraction levels. In subsequent experiments, the subjects maintained constant effort against resistance provided by the experimenters.

The stimuli for the H reflex were of 1 ms duration, delivered from a constant current source through bipolar electrodes, with the cathode proximal. The use of a remote anode on the opposite side of the limb (Hugon, 1973) was avoided because the purpose was to reproduce the conditions likely to be used in diagnostic studies. The cathode was sited in the low popliteal fossa for soleus, behind the head of the fubula for tibialis anterior, over the median nerve medial to the tendon of biceps brachii for the flexor carpi radialis, and over the median nerve at the proximal crease of the wrist for abductor pollicis brevis. Stimulus repetition rate varied with experimental protocol, from once every 10 s (0.1 Hz) to four times per second (4 Hz). The stimuli for F wave studies were pulses of 0.2 ms duration, supramaximal for the direct motor response, delivered at 1 Hz.

For each stimulus level, stimulus rate or contraction level, the H reflex responses were averaged using a sampling rate of 20 kHz. The number of sweeps averaged varied with the signal-to-noise ratio, between 16 (for soleus) and 64–256 (for abductor pollicis brevis). When the H reflex was elicited during a background contraction of the test muscle, multiple consecutive averages were performed to ensure accurate measurement of latency (*see* fig. 3).

The latency of the first deflection from baseline, the amplitude and the area of the evoked H responses were measured using cursors. The results were similar with the two measures of size. Statistical significance was assessed using a t test for paired data.

RESULTS

Reflex responses could be recorded reliably in all subjects from soleus and the forearm flexor muscles when the test muscles were relaxed and from tibialis anterior, flexor carpi radialis and abductor pollicis brevis when the subjects maintained a steady voluntary contraction of the test muscle. These responses were identified as H reflexes using the following criteria: (1) appearance at lower stimulus intensities than the direct motor response (M wave); (2) amplitude greater than that of the M wave with submaximal stimuli; (3) increase and then decrease in amplitude as the M wave increased with progressively increasing stimulus intensities; (4) latency appropriate for an oligosynaptic spinal reflex with fast afferent and efferent pathways (figs 1, 2; Table 1). The first criterion could not be satisfied in all recordings, particularly with studies of the relaxed flexor carpi radialis (4 subjects) and occasionally with the other muscles (e.g., upper traces in fig. 1B).

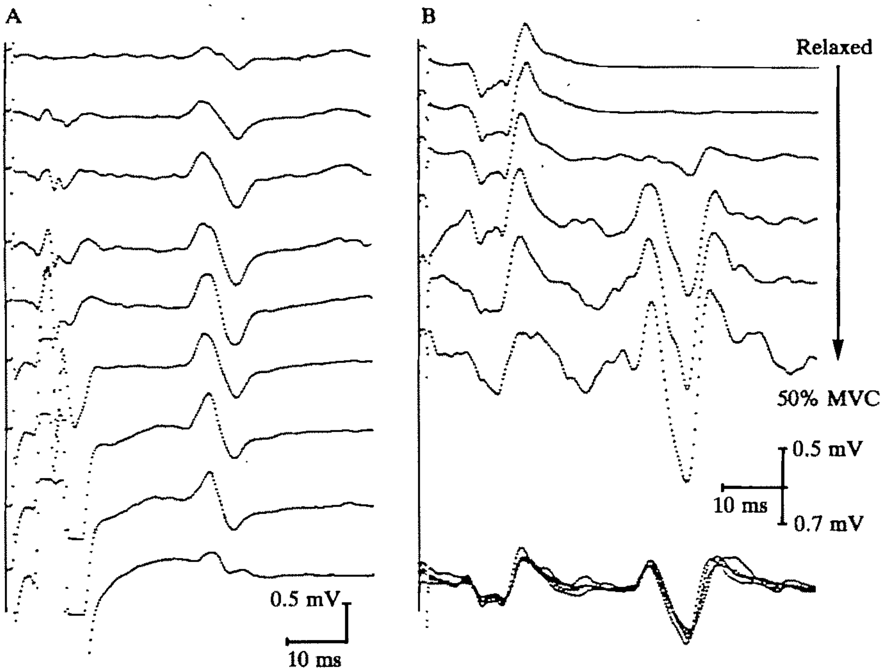

FIG. 1. H reflexes of abductor pollicis brevis (A) and of tibialis anterior (B). The responses in A were recorded during a steady contraction in response to progressively increasing stimulus intensities delivered at 4 Hz. In B, a constant stimulus of 4 mA was delivered at 4 Hz during varying levels of background contraction, ranging from relaxed (*upper trace*) to 40–50% maximal voluntary power (*sixth trace*). The lowest traces contain four superimposed averages, recorded during a moderate background contraction. In A and B each trace is the average of 128 responses.

Effects of voluntary contraction of the test muscle

Threshold and amplitude of the H reflex. In no subject could H reflexes be recorded from the relaxed tibialis anterior and abductor pollicis brevis but, in all 10, reflex responses were obtained readily when stimuli were delivered during a steady voluntary contraction of the test muscle. H reflexes were recorded in the median-innervated forearm flexor muscles of all 10 subjects when relaxed (fig. 2) but, in 4, the H reflex did not appear until the M wave as well developed and the onset of the H wave then merged with the end of the M wave. Voluntary contraction of flexor carpi radialis allowed a clear H reflex to be recorded using a lower stimulus intensity in all 10 subjects (fig. 2); such that the onset of the reflex potential could be defined accurately and the latency, amplitude and area measured reliably. The contraction also ensured that the reflex response involved the desired muscle (flexor carpi radialis) rather than one of the other forearm flexor muscles. The duration of the reflex potential was often longer when relaxed than during contraction (*see* fig. 6), perhaps because, when relaxed, the reflex potential appeared in a number of forearm muscles, each with slightly different latency.

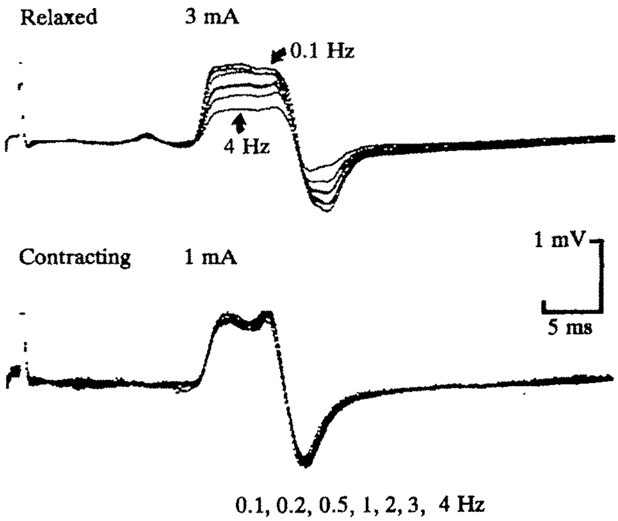

FIG. 2. H reflexes of the forearm flexor muscles/flexor carpi radialis when relaxed (*upper traces*) and during a steady weak contraction of flexor carpi radialis (*lower traces*). The reflex responses evoked by stimuli delivered at seven different rates (0.1, 0.2, 0.5, 1, 2, 3 and 4 Hz) are superimposed. There is a prominent rate-dependent suppression of the H reflex when relaxed but no significant change when contracting. Note that to produce comparable H reflex amplitudes, the stimulus intensities were 3 mA when relaxed and 1 mA when contracting. Each trace is the average of 16–32 responses.

For a constant stimulus intensity, voluntary contraction increased the amplitude of the H reflex of forearm muscles. For abductor pollicis brevis and tibialis anterior, the stronger the background contraction, the greater the size of the H reflex. This is illustrated for tibialis anterior in fig. 1B, using 6 contraction levels, ranging from complete relaxation to approximately 40–50% maximal voluntary power. Stimulus levels for tibialis anterior and abductor pollicis brevis were generally raised until a small but consistent M response was produced and, in weak contractions, the H reflex was then often smaller than the M wave. The identification of the late potential of reflex origin was then confirmed by requesting a stronger contraction or by reducing the stimulus intensity slightly. With weak contractions, the reflex response sometimes appeared in single sweeps to result from stimulus-locked modulation of the on-going volitional EMG rather than

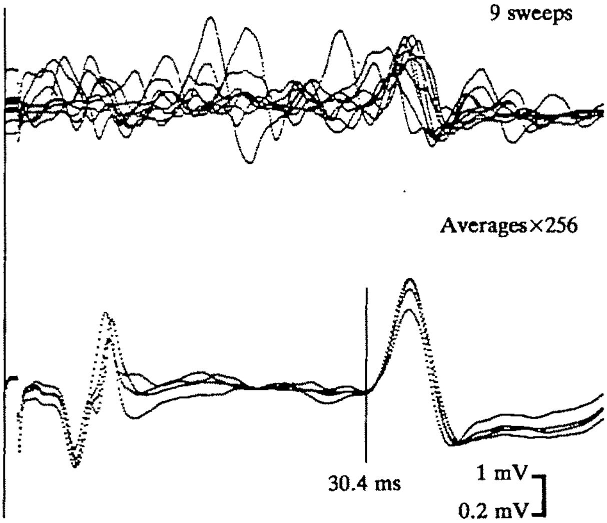

FIG. 3. H reflex of abductor pollicis brevis (same experiment as in fig. 8). *Upper traces*: 9 single sweeps superimposed, showing a clear reflex response that is due to poststimulus modulation of on-going EMG rather than a stimulus-induced recruitment of nondischarging motoneurons. *Lower traces* consist of four averages of 256 sweeps, with the H reflex appearing at 30.4 ms.

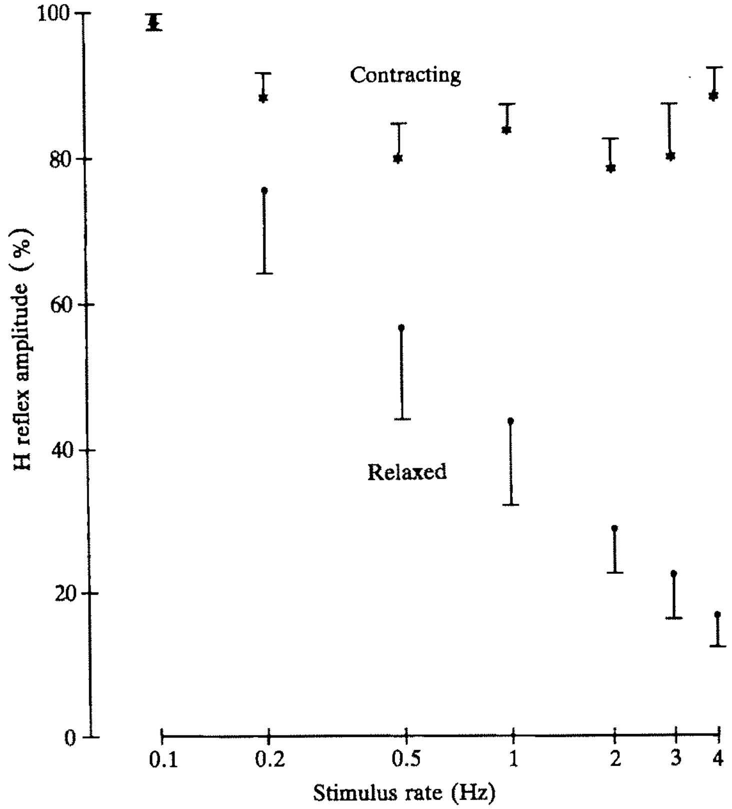

FIG. 4. Low-frequency depression of the H reflex of the forearm flexor muscles/flexor carpi radialis. Pooled data for 6 subjects (mean ± SD). When relaxed there is progressive reflex depression with increasing stimulus rate but, during a steady voluntary contraction, there is little dependence on stimulus rate. For each subject reflex amplitudes have been normalized as a percentage of the largest H reflex in the particular sequence for that subject.

reflex recruitment of inactive motor units (fig. 3). With minor adjustments to the contraction level or stimulus strength, the H reflex appeared in all subjects as a distinct compound EMG potential that stood out from the on-going EMG.

Low frequency depression of the H reflex. The H reflex recorded from the relaxed forearm flexor muscles was attenuated when the stimulus rate was increased from 0.1 Hz to 4 Hz (fig. 2). The data for the 6 subjects in whom the onset of the reflex potential could be defined accurately when relaxed are shown in fig. 4. In confirmation of previous studies (Cook, 1968; Tóth *et al.*, 1979), low-frequency depression was less pronounced with stronger stimuli that produced larger reflex responses preceded by a significant M wave (fig. 5). The strong contraction produced a vigorous forearm movement despite attempts to restrain the limb. The higher stimulus rates induced a rhythmic contraction which appeared to act as a reinforcing manoeuvre, such that individual H waves in a test series became quite variable in size.

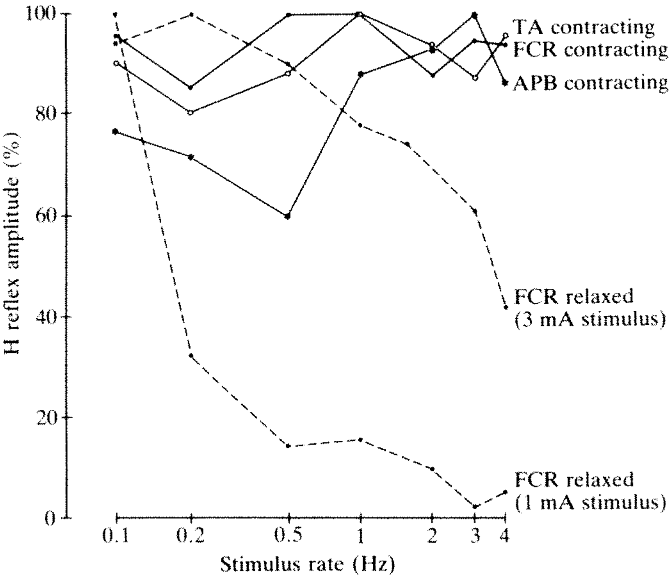

FIG. 5. Low-frequency depression and the effects of voluntary contraction. Data for one subject. When relaxed, the dependence on stimulus rate is more prominent the lower the stimulus intensity. When contracting, there is little dependence on stimulus rate for the 3 muscles examined (tibialis anterior, TA; flexor carpi radialis, FCR; abductor pollicis brevis, APB). For each sequence, the data have been normalized as a percentage of the largest H reflex in that sequence.

In all subjects, low-frequency depression was greatly diminished or abolished when the stimuli were delivered during a steady contraction (fig. 4), the changes being significant for rates greater than 0.5 Hz (P ranging from 0.027 for 1 Hz to 0.0006 for 4 Hz). Similarly, when the stimuli were delivered during steady contraction of abductor pollicis brevis or tibialis anterior, the H reflexes of these muscles did not attenuate as the stimulus rate was increased (fig. 5). All subjects tolerated stimulus rates of 3 or 4 Hz without discomfort, though they found it fatiguing to maintain steady contractions during long averaging runs using low stimulus rates.

Latency of the H reflex. In the group of 10 subjects there was no significant difference in latency of the H reflexes recorded over the forearm flexor muscles whether the subjects were relaxed or contracting flexor carpi radialis (fig. 6). There was also no consistent change in latency with changes in stimulus rate. With abductor pollicis brevis and tibialis anterior, the latency of the smallest discernible reflex response recorded during weak contractions was usually 0.5–1 ms or more longer than that of responses elicited by stronger stimuli or during stronger contractions. With unequivocal reflex responses that fulfilled the criteria for the H reflex, there was no consistent change in latency with contraction strength or stimulus rate. However, with high stimulus intensities, reflex latency increased when the reflex potential decreased in amplitude due to occlusion by the antidromic motor volley.

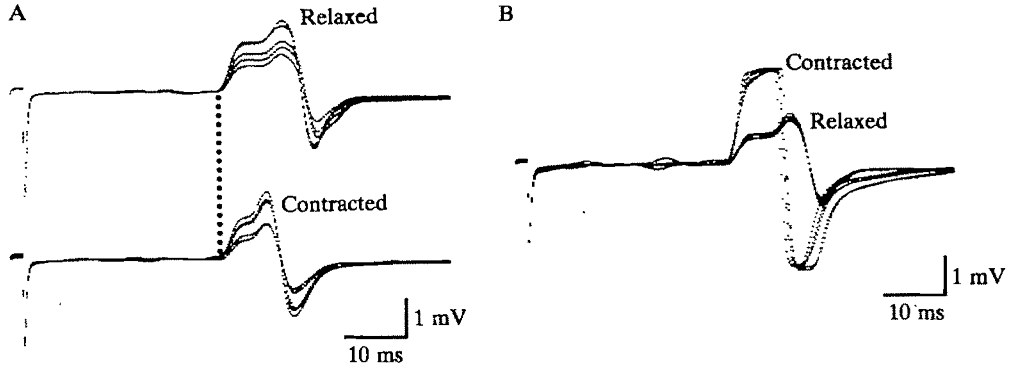

FIG. 6. Effects of a voluntary contraction on reflex latency. A, stimulus intensity adjusted to produce reflexes of comparable amplitude when relaxed (*upper traces*) and when contracting flexor carpi radialis (*lower traces*). B, the same stimulus intensity (4 mA) when relaxed and when contracting. Note the difference in duration of the H waves. Each set of traces consists of 5 averages of, when relaxed, 16 responses elicited at 0.5 Hz and, when contracting, 32 responses at 2 Hz.

Although there was no significant change in the group data, reflex latencies were not constant in individuals with changes in the above parameters. The variable direction of these trends in the individuals rendered the changes in the group data not significant. In one subject, different stimulus intensities resulted in reflex potentials of latency between 15.5 ms and 17.8 ms for amplitudes between 6.8 mV and 0.4 mV, respectively. In the remaining subjects, it was possible to alter the latency of the H reflex in flexor carpi radialis/forearm flexor muscles by up to 0.9 ms (mean 0.4 ms; range 0.3–0.9 ms) by changing the experimental parameters (stimulus rate, stimulus intensity and level of voluntary activity of the test muscle).

In four experiments the effects of a voluntary contraction on reflex latency were examined using (1) constant stimulus levels, and (2) stimulus levels adjusted to produce H reflexes of constant peak-to-peak amplitude. The latencies of the responses seen when relaxed (5 averages, each 16 responses, at 0.5 Hz) were compared with the latencies of responses elicited during a voluntary contraction (5 averages, each of 32 responses at 2 Hz). For 2 subjects there were no significant differences in mean latency or in the variability of latency with either experimental paradigm ($P > 0.2$, fig. 6). For the other 2 subjects the latencies of the H responses recorded during voluntary contractions for the first paradigm were consistently shorter by 0.2–0.3 ms, and these small differences were significant in both subjects ($P < 0.005$).

Comparison of F waves and H reflexes of the same muscles

Minimal F wave latencies. Both the H reflex latency and the minimal F wave latency for abductor pollicis brevis, tibialis anterior and soleus were significantly correlated with subject height (fig. 7), the correlation sufficient to account for 58–93% of the variance in latency (Table 2). In this small group with a restricted age range, neither latency was significantly correlated with subject age (*cf.*, however, Schimsheimer *et al.*, 1987). For each muscle there was a stronger correlation between H reflex latency and F wave latency than there was between either latency and height (Table 2), suggesting that height was not the sole common factor between the H reflex and the F wave.

Given that for abductor pollicis brevis and tibialis anterior, the amplitude of the largest reflex response never exceeded 20–30% of the maximal M wave, this

TABLE 1. H REFLEX AND F WAVE LATENCIES*

	Abductor pollicis brevis		*Tibialis anterior*		*Soleus*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*
H	28.1	24.6–31.1	31.6	27.2–37.5	29.5	25.9–33.9
F min	25.9	23.0–28.4	30.5	26.4–35.5	29.4	25.3–34.0
H-F min	2.2	1.1– 3.8	1.0	0– 3.4	0.1	(−0.8)–(+1.1)
F mean	27.5	24.1–30.1	33.0	28.3–39.3	30.8	26.6–36.1
F max	30.4	26.2–34.7	38.6	32.8–45.3	33.0	28.8–39.7
F max–F min	4.5	2.6– 6.3	8.0	4.1–11.0	3.6	2.3– 5.7
Fastest MCV	59.2	55.7–64.6				
Slowest MCV	50.4	45.4–58.1				
Range MCV	8.8	6.5–10.7				

* Latency is in ms. Motor conduction velocity (MCV) is in $m \cdot s^{-1}$. The slowest MCV has been calculated from the fastest MCV and F max–F min.

TABLE 2. H REFLEX AND MINIMAL F WAVE REGRESSIONS

	Abductor pollicis brevis		*Tibialis anterior*		*Soleus*	
	H	*F*	*H*	*F*	*H*	*F*
Relationship to height						
Correlation coefficient	0.8856	0.7630	0.9056	0.8701	0.9558	0.9622
% variance	78.4%	58.2%	80.2%	75.7%	91.4%	92.6%
Significance	< 0.002	< 0.02	< 0.001	< 0.002	< 0.001	< 0.001
Relationship H : F						
Correlation coefficient	0.9331		0.9506		0.9850	
% variance	87.1%		90.4%		97%	
Significance	< 0.001		< 0.001		< 0.001	

common factor is unlikely to be an identical efferent limb. As illustrated in fig. 3, the motoneurons contributing to the H reflex are those recruited at relatively low thresholds, presumably not the ones responsible for the minimal F wave latency. For abductor pollicis brevis and tibialis anterior in each subject the minimal F wave latency was shorter than the H reflex latency ($P < 0.001$ and < 0.01, respectively; compare figs 3 and 8) but for soleus the latencies were identical (Table 1).

The regression equations for the H reflex and minimal F wave latencies were similar for the two lower limb muscles ($H_{SOL} = 3.13 + 0.90\ F_{SOL}$; and $H_{TA} = 3.05 + 0.93\ F_{TA}$) but both differed from the equation for the thenar muscles ($H_{APB} = -0.11 + 1.09\ F_{APB}$). Assuming that the spinal mechanisms are similar,

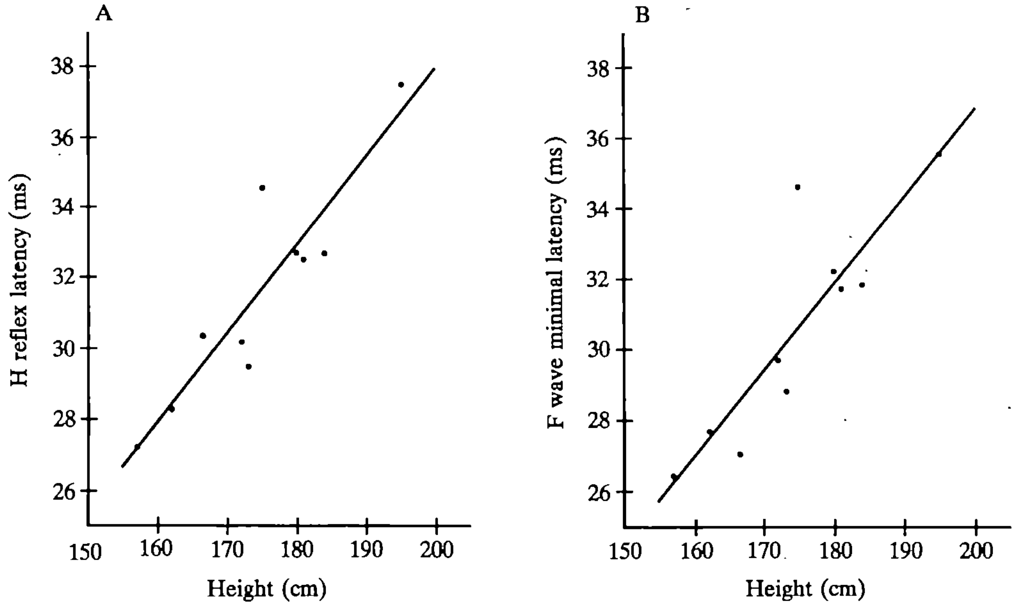

FIG. 7. Relationship between the latencies of the H reflex (A) and the minimal F wave (B) of tibialis anterior and the height of the subjects. Statistics for the regression are given in Table 2.

the differences in the upper and lower limb equations suggest that the relation between the afferent and efferent conduction velocities is not the same in the upper and lower limbs.

Spread of F wave latencies. For abductor pollicis brevis, tibialis anterior and soleus, F waves were recorded in response to at least 50 consecutive supramaximal stimuli (fig. 8). With the thenar muscle, F waves occurred in response to > 80% stimuli and, with soleus, they occurred with all stimuli. However, with tibialis anterior, F waves were elicited by approximately 50% stimuli, presumably reflecting a low excitability of the motoneuron pool. In 2 subjects the F wave 'persistence' for tibialis anterior was 26% and 34%, and the values in Table 1 for these 2 subjects are therefore based on 100 stimuli.

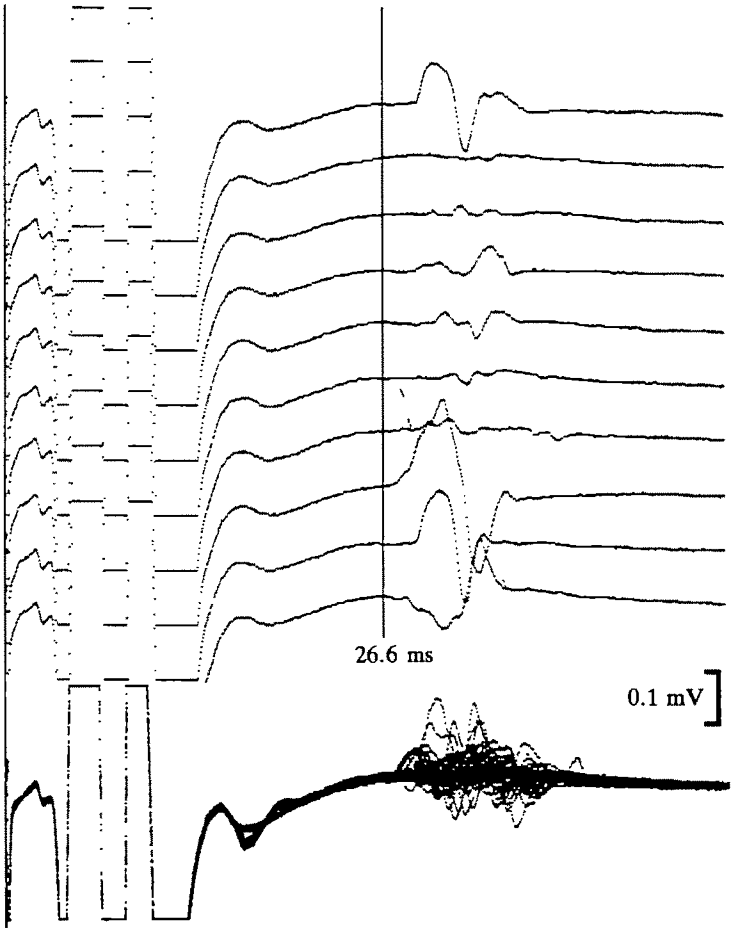

FIG. 8. F waves of abductor pollicis brevis (same experiment as for fig. 3). The upper sweeps show 10 successive responses with the vertical line aligned against the minimal F wave latency (26.6 ms). The lowest sweep contains the responses to 50 consecutive stimuli. Latencies were: F min 26.6 ms; F max 31.4 ms; F mean 28.5 ms; SD 0.915 ms. Note the discrepancy between H reflex latency (30.4 ms, *see* fig. 3) and minimal F wave latency (26.6 ms).

In each subject the spread of F wave latencies was least for soleus (mean 3.6 ms, range 2.3–5.7 ms), intermediate for abductor pollicis brevis (mean 4.5 ms; range 2.6–6.3 ms), and greatest for tibialis anterior (mean 8.0 ms; range 4.1–11.0 ms). These differences between tibialis anterior and the other two muscles were significant ($P = 0.0002$ for soleus; $P = 0.0045$ for abductor pollicis brevis). The low variability in latency of consecutive F waves in soleus suggests that the measured latencies came from a more homogeneous population of efferents than is the case with tibialis anterior. However, the minimal F wave latency was shorter in each subject for soleus than for tibialis anterior (Table 1). It is therefore unlikely that the homogeneous efferent population responsible for the low latency variability for soleus consisted of slowly conducting efferents associated with a pool of small type S motoneurons. The stimulus site for the studies on tibialis anterior was 4–6 cm distal to that for the studies on soleus. The difference in their minimal F wave latencies (1.1 ms) can therefore be explained by peripheral factors without need to postulate that the fastest efferent axons innervating soleus and tibialis anterior differ in conduction velocity.

Comparison of the latency values in Table 1 indicate that the maximal F wave latency for soleus was similar to the mean F wave latency for tibialis anterior, as if a slowly conducting population of efferents were not contributing to the soleus values. There are two likely reasons for this. First, the reflex discharge in the lower-threshold motoneurons with slowly conducting efferents would collide with the antidromic volley and prevent F waves in these motor units. Secondly, the high resting excitability of the soleus motoneuron pool could result in complex F waves consisting of the potentials of more than one motor unit. In this case the measured latency would reflect conduction in the fastest of the discharging efferents. The latter possibility is unlikely to be the sole factor because occasionally longer latencies would be recorded merely by chance.

It is concluded that the F waves of soleus are generated by the faster conducting efferents in the soleus pool, not those explored by the H reflex.

Estimates of the range of motor conduction velocities. With abductor pollicis brevis, the F wave persistence of less than 100% suggests that many of the recorded F waves arose from single motor units. If F waves occur with equal probability in all motoneurons of this pool (Kimura *et al.*, 1984; however, *cf.* Fisher, 1982, 1983), the minimal and maximal F wave latencies could represent conduction in the fastest and slowest motoneurons in that pool. To check whether this is so, the fastest motor conduction velocity over the elbow to wrist segment was determined for each of the 10 subjects (mean 59.2 $\mathrm{m \cdot s^{-1}}$; Table 1). Assuming that this velocity represented the conduction velocity of the axon responsible for the minimal F wave latency, the conduction velocity corresponding to the maximal F wave latency was calculated. In this calculation, no allowance was made for distal latency (an unknown factor for the maximal F wave latency) but 1 ms was subtracted from each latency to allow for the 'turn-around time' at the motoneuron.

The slowest motor conduction velocity for alpha motor axons of the median nerve calculated from F wave latencies was, on average, 50.4 $m \cdot s^{-1}$, giving a spread of conduction velocities of 8.8 $m \cdot s^{-1}$ (range 6.5–10.7 $m \cdot s^{-1}$). These values significantly underestimate the generally accepted range derived using other techniques (e.g., Thomas *et al.*, 1959; Lee *et al.*, 1975; Caddy *et al.*, 1981; Dorfman, 1984; however, *cf.* Hopf, 1963; Ingram *et al.*, 1987). A more acceptable distribution of motor conduction velocities would be 40–60 $m \cdot s^{-1}$. Based on F min of 25.9 ms, this range would correspond to a spread of F wave latencies of 12.5 ms (and thereby to F max of 38.4 ms). It is concluded that, although the relatively simple F wave technique may give useful information about a range of motoneurons in the thenar pool, it may not adequately explore conduction in those with the slowest efferent axons.

DISCUSSION

The present study has demonstrated that H reflexes can be obtained from contracting muscles in upper and lower limbs, that rapid stimulus rates are as effective as slow rates when the relevant muscle is contracting, and that these conditions do not alter the latency of the reflex significantly. These findings extend the diagnostic utility of H reflex testing. However, to maximize the value of reflex studies, the effects of height and those of age (*see* Schimscheimer *et al.*, 1987) must be taken into account in setting normal limits.

The study has established a number of advantages to testing the reflex pathway when the relevant muscle is contracting. First, the amplitude of the reflex response is increased and responses can be obtained at lower stimulus intensities. As a result, the onset of the H wave can be distinguished more easily from the end of the M wave, and latency measurements made more accurately. Secondly, higher stimulus rates can be used because the attenuation of reflex amplitude with rate is greatly diminished. Perhaps this is just as well: few patients would willingly maintain a contraction for the time necessary to define the onset latency accurately during a voluntary contraction if stimulus rates of less than 1 Hz were to be used. Thirdly, the contraction 'directs' the reflex response to the active motoneuron pool so that specific reflex arcs (and specific segmental levels) can be investigated. Finally, the contraction does not impair the accuracy with which latency can be measured. It is, however, reasonable to ask whether H reflex studies can provide data not available from other diagnostic tests such as somatosensory evoked potentials (SSEPs) and F waves.

Comparison with somatosensory evoked potentials

The relationship between the size of the responsible nerve volley and the size of evoked cerebral potential is not linear (e.g., Debecker and Desmedt, 1964; Lesser *et al.*, 1979; Eisen *et al.*, 1982; Gandevia and Burke, 1984). A reduction of the afferent volley by some 50% produces a reduction of the SSEP by only 10%. For pathology to be detectable on amplitude criteria, an asymmetry of greater than 50% is necessary, but this would require a nerve volley of only 10–20% normal size (Gandevia and Burke, 1984). If 10–20% of the sensory fibres innervating the test region are spared the SSEP will have a normal latency and will be within normal limits for amplitude.

This property of the SSEP confers advantages and disadvantages. The major advantage is that the evoked potential is resistant to peripheral pathology and can therefore be useful in circumstances when peripheral nerve volleys are difficult to define (Noël and Desmedt, 1980). However, this property is a disadvantage when trying to define a subtle lesion that is producing few clinical changes, if any. On the other hand, the H reflex depends on a synchronized afferent volley reaching the motoneuron pool and on the resultant excitation being sufficient to discharge motoneurons in the pool. Any pathology that prevents conduction in some afferent axons or increase the dispersion of the afferent volley could increase reflex latency or abolish the reflex discharge.

Comparison with F wave studies

The reflex study can also provide information on motor conduction, but it does so for a select group of motoneurons, those of small size with relatively slowly conducting axons. Reflex latencies cannot be compared with F wave latencies, because the minimal F wave latency probably reflects conduction in the fastest motor axons. Measurements of the minimal, maximal and mean F wave latencies and of F wave persistence provide information about conduction in a number of motor units in the pool. At least for some muscles, the range of F wave latencies probably underestimates the expected latency difference between the fastest and slowest motor units by as much as 50% (*see* Thomas *et al.*, 1959; Lee *et al.*, 1975; Caddy *et al.*, 1981; Dorfman, 1984; *cf.*, however, Hopf, 1963; Ingram *et al.*, 1987). Although F waves *may* occur in all motoneurons in the thenar pool (Kimura *et al.*, 1984), they rarely do so in practice, at least when 50 responses are analysed. In this regard it is relevant that Panayiotopoulos (1979) recommended analysis of 100 responses if the true spread of F wave latencies is to be determined for the intrinsic muscles of the foot. However, few laboratories seem to have adopted this advice.

With motoneuron pools, such as soleus, which can be activated reflexly when relaxed, the reflex discharge would prevent access of the antidromic volley to the reflexly active motoneurons. With such pools, F waves must be confined to motor units that are difficult to recruit in the H reflex. The situation for abductor pollicis brevis (but not tibialis anterior) is likely to be comparable to that for soleus because strong stimuli probably evoke reflex discharges in thenar motoneurons of low threshold when the subject is at rest (*see* Trontelj, 1973) even if the antidromic motor volley prevents their appearance as an EMG potential. It can be concluded that routine F wave studies do not explore conduction in slowly conducting efferents (Fisher, 1982, 1983), the very efferents preferentially accessed in reflex studies.

A major limitation of F wave studies is that, unless collision techniques are used to abolish the M wave (Kimura, 1983), such studies are practical only with the intrinsic muscles of the hand and foot, triceps surae and the pretibial flexors. On the other hand reflex studies can be performed on any limb muscle provided that access can be obtained to the innervating nerve (for the H reflex) or the appropriate tendon (for timed tendon jerk studies, *see* Burke, 1987, and Stam, 1987).

Lack of effect of a voluntary contraction on reflex latency

It is perhaps surprising that, with the exception of liminal reflexes, using a voluntary contraction to raise the motoneuron pool to firing threshold had only minor effects on reflex latency. The absence of a major effect is unlikely to be due to greater difficulty in measuring the latency during a background contraction because the variability of the measurements would then have been greater. A latency shortening might have been expected if higher-threshold, faster-conducting motor units were recruited, but only if the reflex latency was determined by these efferents. However, this is unlikely given the relatively low amplitude of the maximal H response and the likely rise time of the compound EPSP (*see* Burke *et al.*, 1984).

Low-frequency depression of the H reflex

Low-frequency depression of the H reflex of relaxed muscles is generally considered to be a presynaptic phenomenon due to partial depletion of immediately available transmitter stores (Curtis and Eccles, 1960; Čapek and Esplin, 1977; *see also* Van Boxtel, 1986). No satisfactory reason can be advanced to explain why this mechanism would be altered by a voluntary contraction. An isometric voluntary contraction is associated with a fusimotor-driven increase in spindle discharge from the contracting muscle (Vallbo *et al.*, 1979; Burke, 1981). A high-frequency discharge in spindle afferents might act like a tetanic stimulus train to accelerate the processes involved in replenishing transmitter stores. If this were the explanation, driving spindle afferents by vibration of the muscle tendon would also abolish low-frequency depression of the H reflex, but this it does not do (Van Boxtel, 1986). However, with the complex system involved in testing intact human subjects, a number of mechanisms may operate (*see*, e.g., Cook, 1968). It is of interest that habituation of exteroceptive (cutaneous) reflexes is abolished by a voluntary contraction (Desmedt and Godaux, 1976). Rate-dependence is not specific for group Ia reflexes and neither is the effect of voluntary contraction on rate-dependence.

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TIME COURSE OF EFFECTS OF UNILATERAL LESIONS OF THE NUCLEUS BASALIS OF MEYNERT ON GLUCOSE UTILIZATION BY THE CEREBRAL CORTEX

POSITRON TOMOGRAPHY IN BABOONS

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SUMMARY

In order to investigate the effects of a partial cholinergic deafferentation on the functional activity of the cortex, the cerebral metabolic rate of glucose (CMRGlu) was measured with positron emission tomography and ^{18}F-2-fluoro-2-deoxy-D-glucose in 5 baboons (Papio anubis) both before and serially following stereotaxic electrocoagulation of the left nucleus basalis of Meynert (NbM). Four days postlesion, significant metabolic depression was present in the entire ipsilateral cerebral cortex, most marked in the frontotemporal region, and which slowly recovered close to normal within 6–13 weeks. Postmortem studies showed that the lesions were located largely in the NbM, and that a significant decrease in choline-acetyltransferase (ChAT) activity was present in the ipsilateral frontal, temporal and parietal cortices. The animal with the most limited histological lesion showed the least decrease in both ChAT activity and CMRGlu. There was a highly significant linear correlation between the regional cortical decreases in CMRGlu (early postlesion data) and in ChAT activity. These results indicate that cholinergic deafferentation induces a proportional metabolic depression in the cortex. However, compensatory mechanisms operate to restore the cortical metabolic activity gradually despite sustained cholinergic denervation, pointing to pre- and/or postsynaptic adaptation (plasticity). Moreover, unilateral NbM lesions also induced a significant reduction in contralateral CMRGlu, which also demonstrated recovery. Several mechanisms are discussed to explain this contralateral effect, but the most likely implicates a transcallosal depression of function as a result of ipsilateral effects of the NbM lesion. These metabolic effects of cholinergic deafferentation in the primate provide new insight into the mechanisms of cortical dysfunction, and the recovery thereof, following subcortical lesions. In addition, our findings have some relevance to the cortical consequences of cholinergic deafferentation observed in dementia of Alzheimer type.

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INTRODUCTION

The nucleus basalis of Meynert (NbM) is particularly affected by the degenerative processes seen in senile dementia of Alzheimer type (SDAT), and the resulting cortical cholinergic deafferentation is believed to underlie part of the behavioural and neuropathological expression of SDAT, based on extensive clinical, experimental and pharmacological data (for review, *see* Ezrin-Waters and Resch, 1986; Salamone, 1986; Arendash *et al.*, 1987). In rats, large lesions of the basal forebrain, which include the equivalent of NbM, result in a marked but transient cortical metabolic depression (London *et al.*, 1984; Orzi *et al.*, 1986). Since positron emission tomography (PET) studies have also demonstrated cortical hypometabolism in SDAT (Frackowiak *et al.*, 1981; Foster *et al.*, 1984; Haxby *et al.*, 1985; McGeer *et al.*, 1986) we considered it important to establish whether circumscribed NbM lesions in baboons—whose cholinergic system is close to that of man—would have effects similar to those reported in rats. In addition, the latter studies required large groups of rats so as to investigate the regional distribution and the recovery of the cortical metabolic effects. In the present experiments we have used the unique capability of PET to perform sequential studies of regional cerebral metabolic rate of glucose (CMRGlu) in individual adult baboons following stereotaxically placed, NbM lesions. This approach allows the use of each animal as its own control, and the establishment of correlations between any effects of lesions on CMRGlu with neurochemical indices of cholinergic deafferentation measured in the same animal.

In man, lesions of several subcortical nuclei, such as the thalamus and the basal ganglia, induce behavioural impairment suggestive of dysfunction of the cerebral cortex (Feeney and Baron, 1986). Following stereotaxic lesions in the ventromedial thalamic nucleus, autoradiographic studies in rats have shown a widespead reduction in ipsilateral cortical glucose utilization (Girault *et al.*, 1985). PET studies of thalamic or basal ganglia stroke in humans have led to similar findings, providing a metabolic correlate to the observed cognitive disturbances (Baron *et al.*, 1986; Feeney and Baron, 1986; Metter *et al.*, 1986). In addition to the specific implications of this investigation for cholinergic deafferentation in relation to SDAT, the present studies should advance our understanding of the mechanisms involved in the development and recovery of distant functional impairment following discrete subcortical lesions. Finally, we wished to study the feasibility of combining PET technology and postmortem neurochemistry with a specific brain lesion in a limited number of nonhuman primates.

MATERIAL AND METHODS

Animal preparation

Ten adult male baboons (Papio anubis; 12.0–15.7 kg) were used. In 5 the left NbM was lesioned electrolytically under barbiturate anaesthesia (sodium pentobarbital, 20 mg/kg, i.v.). Lesions were made according to the stereotaxic coordinates taken from atlases of the baboon brain (Riche *et al.*, 1968; Satoh and Fibiger, 1985; Davis and Huffman, 1968). The lesion was intended to destroy the left NbM in its entirety by multiple electrode descents. Following a small craniotomy, a bipolar electrode (0.5 mm in diameter) was introduced 10 times between the following coordinates : 17.5–21 mm anterior to the bregma; 9–15 mm lateral to the midline; and -6–$+2$ mm with respect to the interaural plane. A current of 20 mA was applied for 1 min with a commercially available radio frequency lesion generator (Radiobico, Model RFG-4, Radionics). The exposed cortex was covered with a small piece of Spongicel (Spongel, Societé d'Applications Scientifiques et Medicales), virginiamycin was applied topically and the skin incision was sutured. At the time of, and 3 days after the intervention, 0.5 g streptomycin was administered i.m.

Postoperatively, the animals recovered normally from anaesthesia, exhibited no overt neurological or behavioural impairment and maintained their body weight until the end of the experiment.

One baboon was subjected to the same protocol but no current was applied; it will be referred to as a 'sham-operated' animal. Four additional baboons were part of another related protocol but their preoperative PET studies were combined with those of the present study to enhance the statistical power of the control data.

Study protocol and investigations

The regional cerebral metabolic rate for glucose (CMRGlu) was measured by PET using ^{18}F-fluorodeoxyglucose (FDG) as the tracer (Phelps *et al.*, 1979). Each operated baboon was studied before the lesion and 2 to 4 times after surgery at days, 4, 11, 25, 39 or 88.

First, the baboon received 1 mg/kg phencyclidine i.m., and was then brought to the scanning room. There, an i.v. injection of methohexital (Brietal, (Lilly) 4 mg/kg) was performed before tracheal intubation. The animal was then curarized with 0.25 mg/kg of alcuronium (Alloferine, Roche) i.v., and lightly anaesthetized with an i.v. infusion of phencyclidine (7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in saline) and with N_2O in O_2 (66%–33%). This protocol results in a light anaesthesia with the EEG being maintained in stage I–II (Fitch *et al.*, 1978). A catheter was inserted percutaneously into one femoral artery for the sampling of arterial blood for measurement of blood gases, pH, plasma glucose content and radioactivities, and for monitoring of blood pressure. The EEG and ECG were also continuously recorded, and the end-tidal CO_2 content was monitored from the tracheal tube using a Beckman LB-2 analyser. Central temperature was kept within normal limits using a homeostatic heating blanket. The ventilation rate and volume were adjusted to obtain a normal range of $PaCO_2$ and arterial pH.

The baboon's head was carefully positioned in the field of view of the PET camera by means of a specially designed head-holder which included ear-bars and a submandibular orientatable plastic frame such that the scan slices were parallel to the canthomeatal (CM) line. Tattooing of skin landmarks was carried out to further ensure accurate repositioning. The PET camera used was the ECAT II single slice machine, which has a resolution of 19 and 17 mm in the transverse and axial directions respectively (full width at half maximum). Before injection of FDG, transmission data were acquired using a ^{68}Ge-^{68}Ga ring source. Two to 8 mCi of FDG were injected i.v. over 30 s and 12 scans of the selected brain level (CM + 15 mm) were acquired over 56 min using our published protocol (Rougemont *et al.*, 1984). This was a 12 scan sequence with midscan times of 0.5, 1.7, 2.9, 4.2, 5.4, 6.7, 9.0, 12.5, 18.9, 29.6, 42.4, and 56.2 min. This brain level was chosen based on postmortem CM sections of a baboon's brain such that it encompassed the frontal, temporal, parietal and occipital cortices. Following this sequence, 3 other brain sections were also scanned (CM +5 mm, +10mm and +20 mm) to cover the whole brain (10–15 min acquisition time for each section). (Due to the low axial resolution of the camera used, there was considerable overlap between these 4 brain levels.) The arterial FDG history and plasma glucose concentration (mean of 5 determinations at 1, 2, 10, 30, and 60 min) were also obtained (Rougemont *et al.*, 1984). At the end of the PET study, the animal was allowed to recover and returned to its cage.

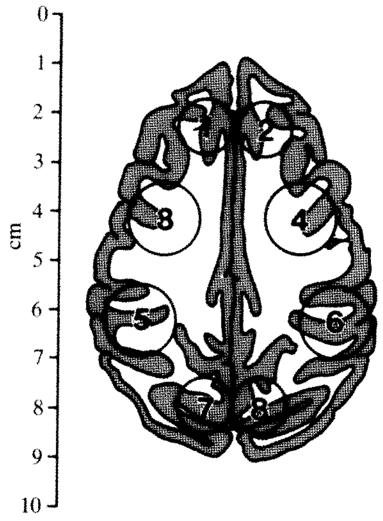


FIG. 1. Diagram showing the Regions of Interest (ROIs) selected for analysis of cerebral glucose utilization, superimposed on the corresponding horizontal section of the baboon brain (canthomeatal line + 15 mm). Following perfusion-fixation, the brain was sectioned horizontally at the same level as that used for the PET image. The ROIs were positioned as follows: 1, 2 correspond to the 'frontal' area; 3, 4 the 'fronto-temporal' area; 5, 6 the 'parieto-occipital' area; and 7, 8 the 'occipital' area. Due to the partial volume effect in PET imaging these ROIs actually sampled a cylindrical block of brain tissue extending almost 10 mm above and below the section shown, and therefore included both grey and white matter generally from more than one lobe, hence the anatomical denomination used for these ROIs.

Determination of regional CMRGlu

Because they were not available from the literature, the FDG transport and phosphorylation rate constants for the baboon's brain were estimated in 1.7 cm^2 circular regions of interest (ROIs) set in the frontotemporal area. The model describing the variation of the regional activity over time contains 3 rate constants (k_1^*, k_2^*, k_3^*) and assumes that no significant dephosphorylation occurs during the first 56 min of the experiment (i.e., $k_4^* = 0$). This assumption is based on extensive biochemical investigations in rats (Nelson *et al.*, 1985) indicating that any glucose-6-phosphatase activity in brain would have only negligible effects within the time frame of the measurement period (i.e., 56 min). Furthermore, were the value for k_4^* in baboons to be meaningfully different from zero, its accurate determination by a 4-constant fitting procedure would require scan times greatly in excess of those employed (Reivich *et al.*, 1982). Also, the model accounts for the brain vascular fraction activity (Vf), and for the delay (dt) between the tracer arrival at the blood and the brain sampling sites and incorporates the integrated nature of the PET data (Mazoyer *et al.*, 1986). A nonlinear least squares algorithm was used to fit this model to the 12 data points of the dynamic series. Due to the limited time resolution of the ECAT-11 tomograph, the dt parameter was fitted separately from the 4 other parameters.

The k_i^* values obtained using this procedure were subsequently used in the 'in vivo autoradiographic' operational equation (Phelps *et al.*, 1979) with the FDG lumped constant (LC) set at 0.42 (Phelps *et al.*, 1979) to transform FDG images so as to obtain tomographic maps of the cerebral metabolic rate of glucose (CMRGlu, in mg · 100 g^{-1} · min^{-1}). This value for the LC, originally determined for the healthy human brain (Phelps *et al.*, 1979) was used here since the corresponding baboon value is unknown and the LC only serves as a scaling factor in the deoxyglucose method. In addition to the frontotemporal area, regional CMRGlu values were measured in various brain areas by means of circular ROIs positioned in the frontal, parieto-occipital and occipital areas, so that they would grossly match the cortical areas taken postmortem for the neurochemical assays (fig. 1).

Statistical analysis

The CMRGlu values were analysed using a two-way analysis of variance with two fixed factors, the region and the time of the measurement. Individual comparisons of means were performed using the Neuman-Keuls procedure (Winer, 1971). Since not all animals were studied at each time interval, the analysis could not assume repeated measurement. Regional left-to-right ratios were analysed using the same methodology.

Biochemical measurements

The baboons were killed by intravenous injection of saturated $MgCl_2$ under Brietal anaesthesia at 49–107 days postlesion. The brain was quickly removed and immediately dissected on ice under continuous humidification of the cortical surface with a fresh oxygenated Krebs solution. Initially, only the frontal cortex was assayed but it became clear the NbM lesions induced widespread and heterogenous effects. Subsequently, therefore, samples from middle frontal gyrus, superior temporal gyrus, the inferior parietal lobe and the superior occipital gyrus were obtained and referred to as frontal, temporal, parietal and occipital cortices, respectively. (Frontal samples were obtained at least 1 cm distant to the electrode insertion in the superior frontal gyrus.) Cortical tissues were immediately frozen on dry ice and kept at −80° C until assayed. ChAT activity was determined according to Fonnum (1975) after homogenization of the tissues in a small volume of Triton/EDTA (0.5%/10 mM, pH 7.4) by sonication, at 4° C. Proteins were measured by the method of Lowry *et al.* (1951). After sampling of the various cortical areas, the brain was sectioned coronally in 4 slices which were individually frozen in isopentane at −45° C. In some animals, cryostat sections (20 μm thick) were obtained at the appropriate level, stained with cresyl violet and examined under the microscope for the precise determination of the emplacement and extent of the lesion. In order to optimize the histological examination, one animal (No. 4) was fixed by perfusion and thus lost for neurochemical analyses.

RESULTS

CMRGlu

1. Due to technical difficulties in obtaining sequential PET data, only 7/10 control studies and 8/17 postoperative studies were suitable for the determination of FDG transport and phosphorylation rate constants (k_i^*). The results are shown in Table 1. The preoperative values (14 hemispheres in 7 animals) were similar to, although more variable than, previously published human data obtained using the same PET scan sequential sampling but a different fitting procedure (Rougemont *et al.*, 1984). The postoperative k_i^* values were found to be slightly, but not significantly, different from the preoperative k_i^* values, both on the side of the lesion and on the opposite side. There were no clear-cut effects of time following lesion on these values. The set of preoperative k_i^* values from the frontotemporal

TABLE 1. RATE CONSTANTS ($k_i^* \cdot min^{-1}$) AND VASCULAR FRACTIONAL ACTIVITY (Vf, ml/ml) IN THE FRONTOTEMPORAL REGIONS*

	k_1^*	k_2^*	k_3^*	*Vf*
Prelesion	0.086	0.116	0.0499	0.057
(n = 14)	±0.007	±0.007	±0.0025	±0.002
Ipsilateral to	0.082	0.134	0.0403	0.058
lesion (n = 8)	±0.004	±0.016	±0.0031	±0.011
Contralateral to	0.090	0.142	0.0468	0.057
lesion (n = 8)	±0.005	±0.014	±0.0028	±0.009

* The values are expressed as mean ± 1 SEM based on the number (n) of values shown in parenthesis.

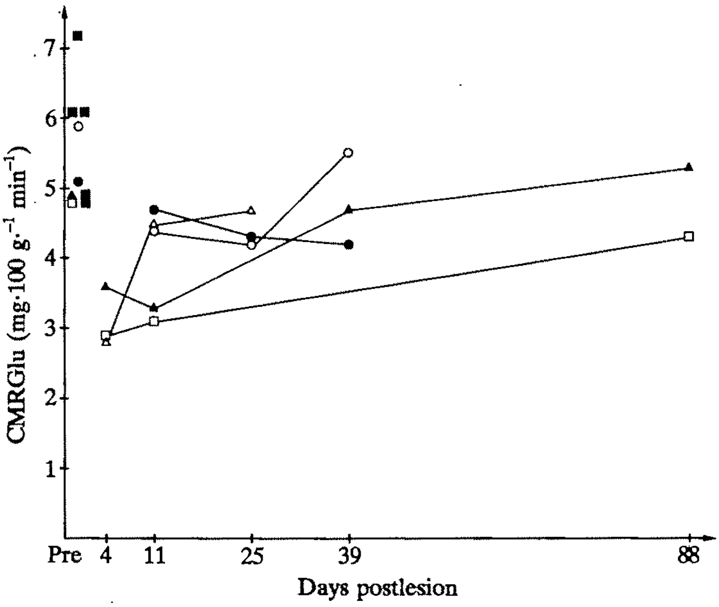


FIG. 2. Temporal evolution of CMRGlu in frontotemporal cortex ipsilateral to the NbM lesion. In individual baboons, each denoted by a different symbol, the time-course of changes in the absolute values for ipsilateral frontotemporal CMRGlu (mg·100 $g^{-1}·min^{-1}$) are shown as a function of days following the electrolytic lesion of the NbM. The preoperative values of 4 of these 5 lesioned animals are also shown (the preoperative data of baboon No. 4 were lost for technical reasons), as well as those of the single sham-operated baboon (*see* Results) and of 4 additional control animals. Baboon No. 1 (open circles), No. 3 (closed circles), No. 4 (open triangles), No. 5 (closed triangles), No. 6 (open squares), Nos 2, 7, 8, 9, 10 (closed squares).

area was therefore used in the 'in vivo-autoradiographic' operational equation to obtain maps of CMRGlu for further analysis of results. This procedure is justified because the method is largely insensitive to small deviations in k_1^* values (Phelps *et al.*, 1979; Huang *et al.*, 1980).

2. Preoperative and control values for all animals are shown in fig. 2 which also demonstrates the individual time course of the effects of left NbM lesion on the ipsilateral CMRGlu in the frontotemporal region, the area most affected by the lesion. There was a striking metabolic depression in the first days postlesion, followed by a progressive recovery towards the prelesion values. Interanimal variations in both the metabolic depression and its recovery were apparent, animal No. 3 in particular, showing only a mild effect of the lesion. The sham-operated baboon could be studied only once postoperatively (at day 4). In the ipsilateral frontotemporal region, the CMRGlu decreased from 4.8 to 4.0 mg · 100 g^{-1} · min^{-1}, indicating that the 'sham operation' in this animal was not devoid of effect. Nonetheless, it is noteworthy that there was no clear-cut decrease in contralateral CMRGlu (*see* below) in this animal.

The analysis of variance (based on all data) revealed significant effects of both the time factor ($P < 0.0001$) and the region factor ($P < 0.01$) with no interaction between these two factors. The *time factor effect* can be summarized as follows: CMRGlu is significantly depressed at day 4 ($P < 0.01$), day 11 ($P < 0.01$) and day 25 ($P < 0.05$) as compared with day 0; recovery is significant from day 11 to day 25 ($P < 0.01$), from day 11 to day 39 ($P < 0.01$), and from day 25 to day 88 ($P < 0.01$). Day 39 and day 88 values are not different from day 0. Table 2 shows a *regional analysis* of these data and confirms that this effect is predominant in the frontal and frontotemporal region. Table 2 also shows that the lesion induced a diffuse bilateral metabolic depression over both hemispheres, most prominent in the ipsilateral frontotemporal cortex, and which recovered in all brain regions analysed, whether ipsilateral or contralateral, anterior or posterior (fig. 3).

TABLE 2. REGIONAL CORTICAL GLUCOSE UTILIZATION (MEAN±SEM) BEFORE AND AFTER AN ELECTROLYTIC LESION OF THE LEFT NUCLEUS BASALIS OF MEYNERT*

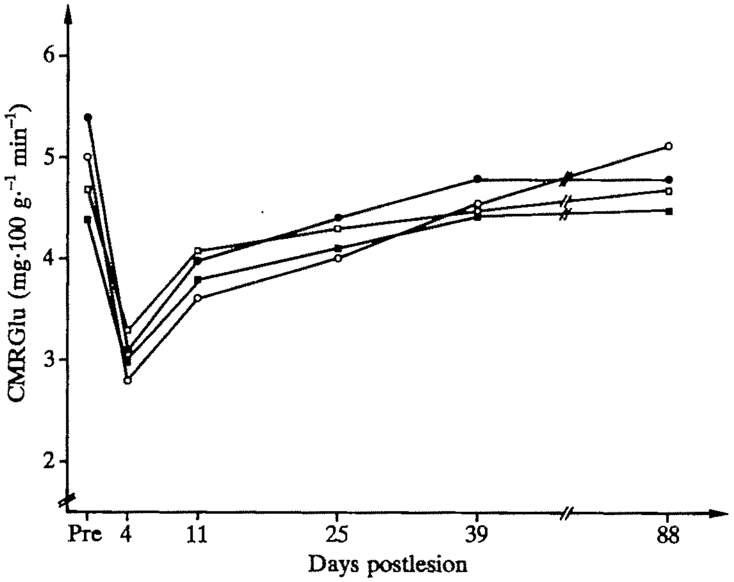
Region of Interest	*Before lesion* ($n = 9$)	*Day 4* ($n = 3$)	*Day 11* ($n = 5$)	*Day 25* ($n = 3$)	*Day 39* ($n = 3$)	*Day 88* ($n = 2$)
Frontal area						
Ipsilateral	5.1±0.3a	2.8±0.4c	3.6±0.2	3.9±0.02	4.4±0.4b	5.1±0.4a
Contralateral	5.1±0.3b	3.2±0.4d	4.0±0.2	4.3±0.1	4.7±0.4	5.2±0.4b
Frontotemporal area						
Ipsilateral	5.4±0.3a	3.1±0.3c	4.0±0.3	4.4±0.2	4.8±0.4b	4.8±0.5b
Contralateral	5.5±0.3b	3.7±0.4d	4.5±0.3	5.0±0.3	5.2±0.3b	5.4±0.7b
Parieto-occipital area						
Ipsilateral	4.8±0.2	3.3±0.3	4.0±0.3	4.4±0.2	4.4±0.5	4.7±0.6
Contralateral	4.7±0.3	3.4±0.4	4.0±0.3	4.4±0.2	4.4±0.5	4.9±0.5
Occipital area						
Ipsilateral	4.4±0.2	3.0±0.4	3.8±0.3	4.1±0.3	4.5±0.7	4.5±0.5
Contralateral	4.3±0.2	3.1±0.4	3.9±0.3	4.2±0.4	4.4±0.7	4.7±0.5

* Values are shown in $\text{mg} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$. Differences are based on analysis of variance such that a = significantly different from day 4 values $P < 0.01$; b = significantly different from day 4 values $P < 0.05$; c = significantly different from prelesion values $P < 0.01$; d = significantly different from prelesion values $P < 0.05$.

The postoperative time course of the individual CMRGlu in each of the 4 brain regions on each side was fitted to the following monoexponential model of recovery:

$$\text{CMRGlu (t)} = a_1 - a_2 e^{-\lambda t}$$

where t = time after lesion (days), a_1 = estimated asymptotic value for CMRGlu ($\text{mg} \cdot 100^{-1}\ \text{g} \cdot \text{min}^{-1}$); a_2 = estimated maximal CMRGlu decrease ($\text{mg} \cdot 100\ \text{g}^{-1} \cdot \text{min}^{-1}$). This fitting procedure disclosed a statistically significant recovery for each one of the 8 brain regions studied (Table 3); the half recovery times



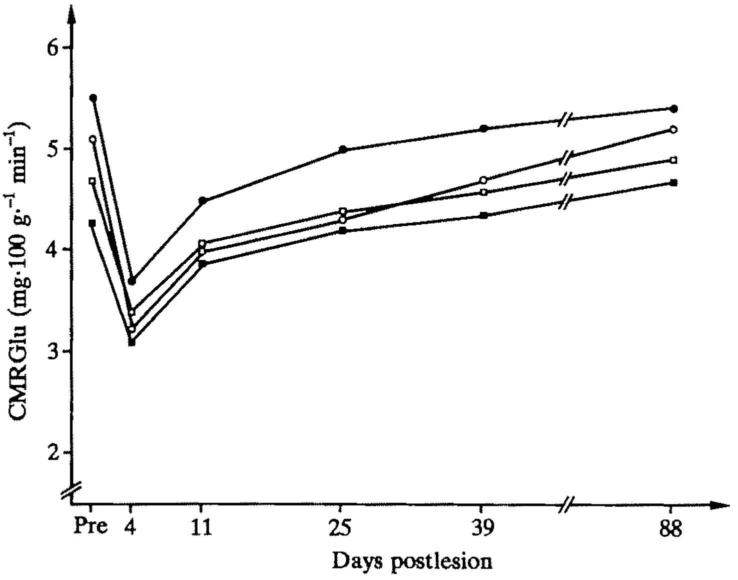


FIG. 3. Evolution of mean values of CMRGlu in four ROIs, ipsilateral (*above*) and contralateral (*below*) to a unilateral lesion of the NbM. Only mean CMRGlu values are shown (*see* Table 2 for corresponding SDs). Frontal (open circles), frontotemporal (closed circles), parieto-occipital (open squares), occipital (closed squares).

revealed a very consistent time course for all brain regions (about 10 days) except for the frontal areas which exhibited a much slower recovery (about 40 days).

3. The mean left-to-right asymmetries for each region and time are shown in Table 4. Analysis of variance on left-to-right ratios shows very significant region

TABLE 3. ESTIMATED MAXIMAL CMRGlu DECREASE, HALF RECOVERY TIMES AND ESTIMATED ASYMPTOTIC (RECOVERY) VALUES FOR CMRGlu IN VARIOUS ROIs FOLLOWING UNILATERAL LESION OF THE NbM

Region of Interest	*Estimated maximal CMRGlu decrease (mg · 100 g^{-1} · min^{-1})*	*Half recovery time (days)*	*Estimated asymptotic values for CMRGlu (mg · 100 g^{-1} · min^{-1})*
Frontal area			
Ipsilateral	−2.60	43.5	5.75
Contralateral	−1.90	29.5	5.44
Frontotemporal area			
Ipsilateral	−1.66	9.5	4.83
Contralateral	−1.58	8.8	5.32
Parieto-occipital area			
Ipsilateral	−1.32	8.4	4.62
Contralateral	−1.37	12.1	4.87
Occipital area			
Ipsilateral	−1.41	9.3	4.50
Contralateral	−1.43	10.6	4.62

TABLE 4. LEFT-TO-RIGHT REGIONAL METABOLIC ASYMMETRY BEFORE AND AFTER LESION OF THE LEFT NUCLEUS BASALIS OF MEYNERT

Region of Interest	*Before lesion ($n = 9$)*	*Day 4 ($n = 3$)*	*Day 11 ($n = 5$)*	*Day 25 ($n = 3$)*	*Day 39 ($n = 3$)*	*Day 88 ($n = 2$)*
Frontal area	1.02a	0.87c	0.91d	0.91c	0.97a	0.97a
	±0.01	±0.03	±0.02	±0.02	±0.02	±0.02
Frontotemporal	1.00	0.85c	0.90c	0.89c	0.93d	0.90c
	±0.01	±0.02	±0.02	±0.02	±0.03	±0.02
Parieto-occipital	1.01	0.96	0.98	0.98	0.98	0.96
	±0.04	±0.03	±0.02	±0.01	±0.03	±0.03
Occipital	1.01	0.96	0.99	0.99	1.02	0.98
	±0.02	±0.03	±0.02	±0.02	±0.02	±0.01

Values are shown as left/right CMRGlu in the stated ROI and are expressed as Mean±SEM. Differences are based on analysis of variance such that a = significantly different from day 4 values $P < 0.01$; b = significantly different from day 4 values $P < 0.05$; c = significantly different from prelesion values $P < 0.01$; d = significantly different from prelesion values $P = 0.05$.

and time effects ($P < 0.0001$). First, the anterior regions are significantly ($P < 0.01$) different from the posterior regions following the lesion. Secondly, in the anterior regions, there are significant asymmetries at day 4 ($P < 0.01$) that disappeared at day 39 ($P < 0.01$) in the frontal area but persisted until day 88 in the frontotemporal area ($P < 0.01$). No significant asymmetries were observed in the 2 posterior regions at any time.

These ratios are biased by the partial volume effect (*see* below) inherent to the imaging procedure, and do not reflect the fact mentioned above that CMRGlu actually decreased on both sides. Nevertheless, the asymmetry analysis is of interest because it further documents that (1) the effects of lesion were maximal in the ipsilateral frontal and frontotemporal regions and (2) recovery to a symmetric CMRGlu occurred in both these regions though was incomplete at day 88 in the latter.

Histology and neurochemistry

1. With the exception of the animal that was perfusion-fixed (No. 4), the histological assessment of the lesion emplacement was carried out on coronal sections of frozen brain. Similar charges were noted in both perfusion-fixed and frozen material. The tracks of the electrolytic lesions were marked by a sometimes intense glial reaction and neuronal loss. When the electrode tracks were in very close proximity to each other a frankly necrotic lesion could be observed. Although the majority of these lesions (10 electrode descents per animal) were situated within the NbM and the substantia innominata, occasional lesions were noted both rostral (in the diagonal band) and superior (in the globus pallidus) to the targeted structure. In 1 of the 5 animals studied (baboon No. 3) almost all the electrode tracks and gliotic changes were situated above the essentially intact NbM, in the overlying globus pallidus, internal capsule and head of the caudate nucleus.

2. *ChAT assays* (*Table 5*). In the side *contralateral* to the lesion, the ChAT activities were consistent from animal to animal despite variations in histological severity of lesion. Highest values were in the temporal cortex, followed by the parietal and frontal cortices, and lowest in the occipital cortex. In the ipsilateral side, there was a marked decrease in ChAT activity in 3 animals (Nos 1, 5, 6), with the most marked effects in the frontal and temporal cortices. Only limited

TABLE 5. ChAT ACTIVITY AFTER LEFT NbM LESIONS

	Killed (days after lesion)	*Frontal cortex*		*Temporal cortex*		*Parietal cortex*		*Occipital cortex*	
Baboon No.		*Ipsilateral*	*Contralateral*	*Ipsilateral*	*Contralateral*	*Ipsilateral*	*Contralateral*	*Ipsilateral*	*Contralateral*
1	49	9.25	15.75	NA	NA	NA	NA	NA	NA
		(−41%)							
3	49	11.75	12.90	NA	NA	NA	NA	8.07	7.68
		(−9%)							
5	107	8.16	15.86	18.07	43.27	11.34	18.43	6.93	6.40
		(−49%)		(−58%)		(−34%)		(+8%)	
6	91	9.60	19.73	18.87	43.05	15.79	27.88	9.14	10.69
		(−51%)		(−56%)		(−47%)		(−14%)	

Values are expressed in nmol Ach formed/mg protein/h. NA = not available. Values in parentheses are percentage decreases in ChAT activity, calculated as (1 − ipsilateral/contralateral) × 100.

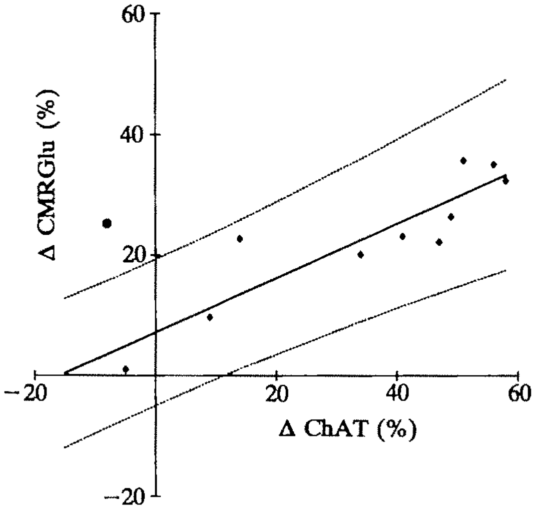


FIG. 4. Early (day 11) decreases in ipsilateral regional CMRGlu as a function of the corresponding regional decrease in cortical ChAT activity (measured in animals 1, 3, 5 and 6 at killing, day 49 to 107, *see* Table 5) following left NbM lesions (n = 11 regional data pairs). The values shown are percentage decreases in regional CMRGlu (with respect to the corresponding regional preoperative value found in the same animal). ChAT activity is expressed as a percentage decrease relative to the non-operated side, in the cortical regions corresponding to the CMRGlu measurements (namely, the frontal, frontotemporal, parieto-occipital, and occipital regions defined for CMRGlu were matched to the frontal, temporal, parietal, and occipital cortices sampled for ChAT activity, respectively). The linear regression was carried out using only 10 data pairs (shown as diamonds), as the deviation for the eleventh data pair (shown as a target) was found outside sampling error at $P < 0.01$ (Snedecor and Cochran, 1980, p. 168). The linear regression calculated was statistically significant ($P < 0.0003$), and according to the equation: Δ % CMRGlu = 0.45 Δ ChAT+7.17. The dotted lines show the 95% confidence limits for the regression line.

reductions in ChAT activity were observed in the occipital cortex. With these 3 animals there was no evident time-dependent difference either in left-to-right ratios of ChAT or the absolute activity in the lesioned hemisphere. Indeed, animals No. 1 and 5, in which ChAT activities were measured at days 49 and 107 postlesion, respectively, exhibited comparable decrease in the lesioned hemisphere. In the last animal (No. 3), there was no obvious effect of NbM lesion on cortical ChAT activity.

CMRGlu-histology-ChAT correlations

Since the histological effects of electrolytical NbM lesions were not quantified, the only noteworthy observation was that the animal with the mildest histological effects (No. 3) also had the least metabolic as well as neurochemical effects of the lesion.

There was a highly significant linear correlation between the relative ipsilateral regional decreases in CMRGlu (measured at day 11 postlesion) and in ChAT activity (measured at killing, day 49 to 107) (fig. 4). There was no such significant correlation either when ipsilateral CMRGlu data at the last PET study (a few days before killing) were used, or when contralateral CMRGlu data were used (whether at 11 days or at the termination of the experiment).

DISCUSSION

This is the first study to investigate the effects of NbM lesions on cerebral glucose utilization in the baboon. In the discussion, other than methodological points, the following issues will be addressed: (1) the ipsilateral cortical metabolic effects that were observed immediately after NbM lesions; (2) the metabolic depression that occurred in the contralateral hemisphere; and (3) the recovery of cerebral glucose use from this experimental subcortical lesion.

Lesion efficacy and emplacement

The emplacement of the electrolytic lesion was studied by histological examination and neurochemical analyses and confirmed lesion efficacy in 4 out of our 5 animals. There was neuronal loss and gliosis in the NbM along the needle tracks in these 4 animals, without significant lesions elsewhere. In the 3 animals of this group that were subjected to neurochemical analysis, there was a marked decrease in cortical ChAT activity ipsilateral to the lesion (Table 5). In 1 animal (No. 3), however, most of the needle tracks were located outside the NbM, and this animal had only a very mild decrease in ChAT activity.

In the hemisphere *opposite* to the lesion, measured ChAT activity was consistent from animal to animal regardless of the severity of the lesion. Based on rat studies in which basal forebrain lesions were without effect on contralateral ChAT activity (Pepeu *et al.*, 1985), again the contralateral values could be considered as being normal in our animals. Furthermore, the contralateral ChAT values showed a regional distribution (highest in temporal and lowest in occipital cortex) which agrees with the known density of cholinergic projections from the NbM in primates (Mesulam *et al.*, 1986*a*) and with regional ChAT levels reported in the normal cortex of rats (Pepeu *et al.*, 1985) and primates (Ridley *et al.*, 1985, 1986; Struble *et al.*, 1986).

Ipsilateral to the lesion we found a decrease in ChAT activity of about 40–50% in the 3 affected animals, indicating an effective, although incomplete, cholinergic deafferentation of the neocortex. The magnitude of this effect as well as its predominance in the fronto-temporal-parietal cortex is very similar to previous data from rat and primates (Pepeu *et al.*, 1985; Ridley *et al.*, 1985, 1986; Struble *et al.*, 1986). Our results further show that the effects of NbM lesion on cortical ChAT activity are long lasting since a marked decrease in activity was still present 107 days postsurgery, consistent with the very slow or even inapparent recovery of this neuronal cholinergic marker in rats (Pepeu *et al.*, 1985).

Ipsilateral, early, cortical metabolic effects

In spite of the small number of baboons studied, the present investigation demonstrates that lesions essentially confined to the NbM induce marked decreases in ipsilateral cortical glucose utilization in nonhuman primates. Compared with preoperative and control studies, the metabolic depression was most prominent in frontal and frontotemporal regions and least in parietal and occipital regions (mean decrease at day 4, 45%, 42%, 34% and 32%, respectively). Unilateral basal forebrain lesions in rats, result in similar effects, both in magnitude and regional distribution, on ipsilateral cortical CMRGlu (London *et al.*, 1984; Orzi *et al.*, 1986). The significant linear correlation found between the ipsilateral regional decreases in CMRGlu (day 11 postlesion) and ChAT activity (fig. 4) indicates that the immediate, metabolic cortical effects of NbM lesions were proportional to the degree of cholinergic deafferentation achieved. The cholinergic input from the NbM therefore appears to exert a significant influence on cortical metabolic activity, consistent with (1) the desynchronization of cortical activity that this transmitter appears to mediate (Levey *et al.*, 1987); (2) the evidence that acetylcholine acts as an excitatory neuromodulator via conventional synapses (Rigdon *et al.*, 1986; Sato *et al.*, 1987); and (3) the fact that muscarinic antagonists depress, while muscarinic agonists and anticholnesterase agents enhance, cortical glucose utilization (Weinberger *et al.*, 1979; Helén and London, 1984; Harrell and Davis, 1985; Soncrant *et al.*, 1985; Hoffman *et al.*, 1986; Churchill *et al.*, 1987). Following lesions of the septum or fimbria-fornix transection in rats, there is a decrease of glucose utilization in the deafferented sectors of the hippocampus (Harrell and Davis, 1984, 1985; Kelly *et al.*, 1985) that is linearly correlated with the depression in acetylcholine esterase (Kelly *et al.*,1985). Motohashi *et al.* (1986*a*) have reported a linear correlation between the depression in CMRGlu and the decrease in ChAT activity in the interpeduncular nucleus of rats 14 days after lesions of the lateral habenula. In contrast, experimental lesions of other ascending subcortico-cortical systems—namely the locus coeruleus, the mesocortical dopaminergic and the rostral raphe systems—have only little or undetectable effects on cortical glucose utilization (Kozlowski and Marshall, 1983; McCulloch, 1982; Savaki *et al.*, 1984; Cudennec *et al.*, 1988). These independent studies further support the hypothesis that the cortical hypometabolism subsequent to NbM lesions can be attributed to the cholinergic system and does not result from incidental damage to ascending monoaminergic pathways.

The only 'sham-operated' baboon did show some metabolic depression ipsilateral to the needle descents, but the effect was much less pronounced than that seen in effectively lesioned animals (20% in the frontotemporal cortex at day 4). This mild metabolic depression is consistent with that reported in sham-operated rats by London *et al.* (1984). It is therefore possible that part of the metabolic depression found in truly lesioned animals, particularly in the frontal cortex, may be secondary to 'nonspecific' surgical interference. In 1 of the 5 animals studied (baboon No. 3), however, almost all the electrode tracks and gliotic changes were sited above the, essentially intact, NbM: this animal had a minimal decrease in ChAT activity (−9%) and the least changes in CMRGlu (fig. 2).

Contralateral cortical metabolic effects

Our data suggest that unilateral NbM lesions also result in a smaller but still significant metabolic depression of the contralateral cerebral hemisphere (Table 2, fig. 3). As in the ipsilateral cortex, this effect predominated in the frontal and frontotemporal regions (mean CMRGlu decrease at day 4: 37% and 30%, respectively). Because of the poor spatial resolution of the PET camera used with respect to the size of the baboon's brain, this contralateral metabolic depression could represent a partial volume artefact from the lesioned hemisphere. Specially designed phantom studies showed that this artefact probably explains part of the contralateral effect, especially in the frontal and occipital areas because of their anatomical proximity. It probably also resulted in underestimation of the left-to-right metabolic asymmetries (Table 3). However, there can be no doubt from phantom data, as well as from our regional metabolic data in the frontotemporal and parieto-occipital ROIs (which were positioned several centimetres apart, fig. 1), that NbM lesions do induce a significant contralateral metabolic depression. The autoradiographic data of London *et al.* (1984) indicate a similar, although less prominent, contralateral effect in unilaterally NbM lesioned rats.

This contralateral effect may represent a nonspecific consequence of the surgical trauma; however, its protracted time course (fig. 3) and the fact that it was virtually absent in animal No. 3 and in the 'sham-operated' baboon argue against this interpretation. It could also be due to contralateral projections from the NbM, which are known to exist in primates (Pearson *et al.*, 1983) and probably also in rats (Pearson *et al.*, 1985, 1986, 1987). However, these direct contralateral projections are very sparse and would probably not explain the observed metabolic effects. In addition, unilateral basal forebrain lesions, in rats, do not reduce ChAT in the contralateral cortex (Pepeu *et al.*, 1985, 1986), as would also appear to be the case from our data (Table 5). To explain this contralateral metabolic depression, we would favour a transcallosal effect secondary to the ipsilateral depression of cortical function—'diaschisis' (Feeney and Baron, 1986). A similar transneural mechanism has been proposed to account for the contralateral cortical hypometabolism constantly observed in rats and humans after thalamic lesions (Girault *et al.*, 1985; Baron *et al.*, 1985; Cambon *et al.*, 1987).

Recovery of cortical metabolism

Following the initial marked depression of glucose utilization in the ipsilateral cortex, a clear-cut glucose metabolic recovery was demonstrated in our NbM lesioned baboons (fig. 3, Table 2). This process occurred in every brain region analysed and was near asymptotic within 3 months although the persistance of a slight left-to-right asymmetry in the frontotemporal area at day 88 (Table 3) suggests that residual metabolic sequelae were still present. The rate of recovery was consistent among all brain regions except in the ipsilateral frontal cortex where it was much slower (Table 4), perhaps in part because of the direct trauma from needle insertion. In rats with unilateral basal forebrain or medial septal lesions, the metabolic effects of cholinergic deafferentation consistently recover within 1 to 3 months (Harrell and Davis, 1984; London *et al.*, 1984; Orzi *et al.*, 1986). A similar recovery of cortical glucose utilization after subcortical lesions has been demonstrated in the adult human brain (Feeney and Baron, 1986), especially after thalamic lesions (Baron *et al.*, 1986). As in the case of thalamic lesions, the behavioural consequences of NbM lesions (Dubois *et al.*, 1985) have been reported to recover in marmoset monkeys (Ridley, 1985, 1986) and rats (Bartus *et al.*, 1985), despite apparently sustained cortical cholinergic denervation.

There are a number of possible mechanisms that could explain this metabolic recovery, all of which implicate a compensation or adaptation to deafferentation as a sign of plasticity of the mature cerebral cortex. Cholinergic reinnervation of the cortex would stand as one straight-forward possibility consequent upon sprouting either from residual intact neurons in the lesioned NbM, or from the contralateral NbM, and/or from other cholinergic (including intrinsic cortical) neurons. However, there was no normalization of ChAT activity levels up to 109 days postlesion, and the final ChAT values were similar to those reported in the acute phase in rats and monkeys (Pepeu *et al.*, 1985; Ridley, 1985, 1986; Struble *et al.*, 1986). In most rats studies of unilateral nucleus basalis lesions, recovery of ChAT is very slow or absent (Pedata *et al.*, 1982; Bartus *et al.*, 1985; El-Defrawy *et al.*, 1986; Wenk and Olton, 1984), although possibly dependant on the animal's age (Höhmann *et al.*, 1987); more inconsistent results have been reported regarding other cholinergic markers (Pedata *et al.*, 1982; Bartus *et al.*, 1985; El-Defrawy *et al.*, 1986; Gardiner *et al.*, 1987). Our results thus indicate that the return to normal energy metabolism occurred despite sustained cholinergic deafferentation. Following medial septal lesions in rats, recovery of CMRGlu in the hippocampus also took place despite a persistent decrease in acetylcholinesterase activity (Harrell and Davis, 1984). In the chronic stage, therefore, only pharmacological or behavioural challenge may be able to unmask metabolic stigmata of cholinergic deafferentation (London *et al.*, 1984).

If the metabolic recovery is not due to cholinergic reinnervation what could be the mechanisms involved? An adaptation within the cholinergic projection fields is one possibility (Lamour *et al.*, 1982), perhaps involving hyperactivity of remaining cholinergic terminals and/or alterations in postsynaptic receptors (McKinney and Coyle, 1982). Also, alterations in the GABA, the serotonergic, and the peptidergic cortical systems have been reported after basal forebrain lesions in rats (Höhmann *et al.*, 1984; Pepeu *et al.*, 1986; Wenk and Engisch, 1986; Arendash *et al.*, 1987) and monkeys (Wenk *et al.*, 1986), suggesting a process of transynaptic reorganization. Three additional, though unlikely, hypotheses can be evoked: (1) indirect effects of NbM lesion on the cortical metabolic activity via NbM-thalamic connections (Levey *et al.*, 1987); (2) recovery from damage to noncholinergic neurons in the lesioned NbM (Mesulam *et al.*, 1986*b*); and (3) retrograde effects on cortico-innominatal neurons after damage to their terminals within the NbM (Mesulam and Mufson, 1984; Russchen *et al.*, 1985). Finally, whether any destruction of fibres of passage within the NbM as a result of electrolysis played a role is unlikely as our findings are very similar to two rat studies in which neurotoxins were employed (London *et al.*, 1984; Orzi *et al.*, 1986).

Regardless of the mechanisms in play, the fact that the profound cortical metabolic depression that follows NbM lesions almost fully recovers demonstrates an extremely efficient process of adaptation. Recovery does not occur after deafferentation of the rostral raphe nuclei or the contralateral cerebellum (following lesions of the habenula and the cortico-ponto-cerebellar system, respectively) (Ito *et al.*, 1985; Motohashi *et al.*, 1986*b*; Pantano *et al.*, 1986). Conversely, metabolic recovery seems to be a constant phenomenon in the deafferented cerebral cortex, after, for example, either thalamic lesions (Cambon *et al.*, 1987) or unilateral enucleation (Cooper and Thurlow, 1985). In addition, the present study demonstrates that the contralateral cortical hypometabolism present initially is also subject to full recovery, despite a sustained ipsilateral depression in ChAT activity, in agreement with the suspected transcallosal mechanism for decreased glucose use; parallel findings have been reported in humans with thalamic lesions (Cambon *et al.*, 1987).

In PET studies of patients with probable Alzheimer's dementia, which involves the NbM in addition to other cortical and subcortical neuronal systems, the decrease in cortical CMRGlu predominates in the parietotemporal cortex and worsens with time (Friedland *et al.*, 1985). Our findings are clearly different, both in the topography and time course of the metabolic effects (although the effects of progressive neuronal degeneration and acute electrolytic lesions may not be comparable). The marked parietotemporal hypometabolism in Alzheimer's disease is correlated with a similar topography for both the cortical neuropathological lesions (Friedland *et al.*, 1985; McGeer *et al.*, 1986) and the deficits in somatostatin (Tamminga *et al.*, 1987). Nevertheless, the cholinergic deficit of Alzheimer's disease may be implicated in the diffuse cortical hypometabolism observed in moderate and severe cases as well as in the metabolic reduction sometimes found in the prefrontal cortex (Frackowiak *et al.*, 1981). In progressive supranuclear palsy, where the degenerative process affects several subcortical systems including the NbM, there is a marked prefrontal cortex hypometabolism that is associated with a 'frontal-type' dementia (D'Antona *et al.*, 1985).

Recently, it has been suggested that the neuronal lesions that are found in the cerebral cortex in Alzheimer's disease may in fact be a consequence of the NbM lesions, based on experimental studies in rats (Arendash *et al.*, 1987). Our results may indicate that the capacity to compensate for cholinergic deafferentation that characterizes the healthy cerebral cortex, demonstrated here in young adult baboons, may be lacking in Alzheimer's disease, leading to irreversible metabolic and behavioural deficits and, perhaps, also to secondary neuronal degeneration.

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DISTRIBUTION AND TOXIC EFFECTS OF INTRAVENOUSLY INJECTED EPIRUBICIN ON THE CENTRAL NERVOUS SYSTEM OF THE MOUSE

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SUMMARY

Epirubicin (4′-epi-doxorubicin) is a new anthracycline cytostatic, which was synthesized in an effort to find an agent with an improved therapeutic effect on human malignant tumours combined with reduced myocardial toxicity. Animal experiments have previously shown that the parent drug doxorubicin, besides being a myocardial toxin, may cause nerve cell lesions both in the central and the peripheral nervous system. Intravenously (i.v.) injected doxorubicin passes into regions of the nervous system located outside the blood-brain barrier (BBB); the drug accumulates in the nucleus of neurons and causes cell degeneration. This investigation was performed to establish whether epirubicin, given as a single i.v. injection in the mouse, could enter the central nervous system (CNS) and cause neurotoxic effects. Epirubicin was found to emit a primary orange fluorescence in thin frozen sections. Detectable amounts of epirubicin could not be seen in regions protected by the BBB. The choroid plexus and all the circumventricular brain regions with the exception of the subcommissural organ showed the presence of the drug in the parenchyma and a marked accumulation in cell nuclei. Severe cellular changes were found in these regions by light and electron microscopy and the alterations were most marked in mice with the longest survival period (45 days). The animals also developed a progressive sensory polyneuropathy and appeared lethargic. Epirubicin given as a single i.v. injection in the mouse will thus spread into brain regions lacking a BBB where it produces toxic lesions in the same way as previously reported for the parent compound, doxorubicin.

INTRODUCTION

Anthracyclines are powerful antineoplastic compounds which are widely used in the treatment of malignant tumours. Doxorubicin (Adriamycin) is the anthracycline most commonly chosen. Unfortunately it can induce severe cardiac disturbances, particularly after repeated administrations (Lefrak *et al.*, 1973). Experimental studies have shown that another side-effect may occur in laboratory animals. Thus doxorubicin, which normally cannot pass into regions of the nervous system protected by the BBB, when injected intravenously (i.v.) can diffuse into

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regions lacking a barrier where it causes cell degeneration (Cho, 1977; Merker *et al.*, 1978; Cho *et al.*, 1980; Bigotte *et al.*, 1982*a*, 1984; Eddy and Nathaniel, 1982; Bigotte and Olsson, 1983*a*).

A new anthracycline analogue, 4′-epi-doxorubicin (Epirubicin), differs from doxorubicin in the orientation of the hydroxyl group in the daunosamine sugar moiety (Ganzina, 1983). Clinical and laboratory studies have shown that it is more effective than the parent compound doxorubicin and less cardiotoxic (Arcamone *et al.*, 1975, 1978; Giuliani and Kaplan, 1980). It is not yet known to what extent this compound, after an i.v. injection, can enter the brain, particularly into areas lacking a BBB and whether in such regions it will cause any cell lesions.

The detailed mechanisms by which anthracycline compounds exert toxic effects are still a matter of discussion. Their influence on neurons is probably mainly a consequence of disruption of the DNA helix and an interference with cellular protein synthesis, but changes in membranes and other actions might well contribute to cell degeneration (Schwartz, 1975; Murphree *et al.*, 1976). The interaction of epirubicin and doxorubicin with DNA is believed to be identical and differences in activity must be attributed to variations in pharmacokinetics, metabolism, distribution or other modes of action (Weenen *et al.*, 1984).

The aim of this study was to evaluate to what extent i.v. administered epirubicin enters the CNS of the mouse and whether it will produce toxic effects in circumventricular regions and other parts of the brain located outside the BBB in the same way as previously reported for doxorubicin (Bigotte *at al.*, 1982*a*; Bigotte and Olsson, 1983*a*).

MATERIALS AND METHODS

Twenty-nine adult albino mice of the NMRI strain (Anticimex, Sweden) with weights ranging from 30–32 g were used. One group of mice was used for localization of epirubicin by fluorescence microscopy after i.v. injection and another group was taken for light and electron microscope examination in order to detect structural lesions induced by the drug.

Fluorescence microscopy

One group of 9 animals received an i.v. injection of 0.3 mg epirubicin hydrochloride (10 mg/kg body wt) in 0.15 ml saline. This is a dose comparable to that used in patients for the treatment of malignant tumours. Epirubicin (Farmorubicina) was kindly provided by Carlo Erba Lda, Lisbon, Portugal. The injection was made into an isolated femoral vein under intraperitoneal pentobarbital anaesthesia (40 mg/kg body wt).

The animals were killed 15 min or 2 h after the injection by whole body perfusion of a 10% formalin solution in Sörensen's 0.1 N phosphate buffer, pH 7.4 (Bigotte *et al.*, 1982*a*, 1984). From each mouse the entire brain, the brainstem and the pituitary gland were removed. Portions from the peripheral nervous system were also sampled and the results will be reported separately. Coronal slices were obtained from the brain and the brainstem. Each sample was covered by talc immediately after dissection to avoid freezing artifacts and then rapidly frozen in liquid nitrogen. The specimens were cut into about 7 μm serial sections, using a TEC-II cryostat. A Leitz fluorescence microscope equipped with a 200 W high pressure mercury lamp, a BG 12 excitation, a K 530 or K 510 barrier filter and a dark field condenser was used. Photographs were taken using Kodak Tri-X Pan black and white film.

Light and electron microscopy

One group of 12 mice received an i.v. injection of 0.3 mg epirubicin hydrochloride in 0.15 ml saline. Eight mice were used as controls and received 0.15 ml saline without addition of the drug. The animals were killed at 7, 13, 30 or 45 days after injection. They were reanaesthetized with pentobarbital and whole body perfusion fixation was performed through the heart with a 3% glutaraldehyde solution in 0.1 M cacodylate buffer, pH 7.4, at room temperature. Tissue samples from the pituitary gland, the circumventricular brain regions and the choroid plexus were taken and processed for light or electron microscopical observation (Bigotte *et al.*, 1983*a*).

RESULTS

General observations

The mice which had received epirubicin as a single i.v. injection gradually lost weight. Animals with a survival period of 30–45 days lost approximately 20% of their body weight and at this period 25% of the mice had died. The control mice showed no significant changes in body weight. Special precautions were taken to feed the animals since the mice injected with epirubicin had difficulties in reaching for food and water, normally placed in the upper part of their cages. Mice injected with epirubicin also lost their fur and appeared lethargic, particularly after 30–45 days. They also showed signs of a progressive sensory polyneuropathy and after 30–45 days became unable to stand properly and their limbs had a tendency to splay. The responses to painful stimuli and noise were impaired.

Macroscopical examination of the fixed specimens showed a pronounced reduction in volume of the pituitary at 45 days, but the brain and the brainstem appeared normal.

Fluorescence microscopy

Preliminary experiments showed that epirubicin, with the filter combination used, emitted a primary orange fluorescence which could easily be distinguished from the background and from autofluorescent material.

Particular efforts were made to identify the circumventricular brain regions which are known to be located outside the territory of the BBB (fig. 1). The prechiasmatic region, the neurohypophysis and the pituitary stalk, the pineal gland, the subfornical organ, the median eminence and the area postrema all showed pronounced fluorescence, an expression of the normal high permeability of the vessels in these regions. Illustrative examples are presented in fig. 2.1. The fluorescence was particularly pronounced in the nuclei of the cells. The epithelial cells of the choroid plexus showed pronounced nuclear fluorescence (fig. 2E) and some of the ependymal cells close to the circumventricular organs also displayed orange nuclear labelling. The subcommissural organ and all brain regions located within the territory of the BBB showed no signs of epirubicin fluorescence.

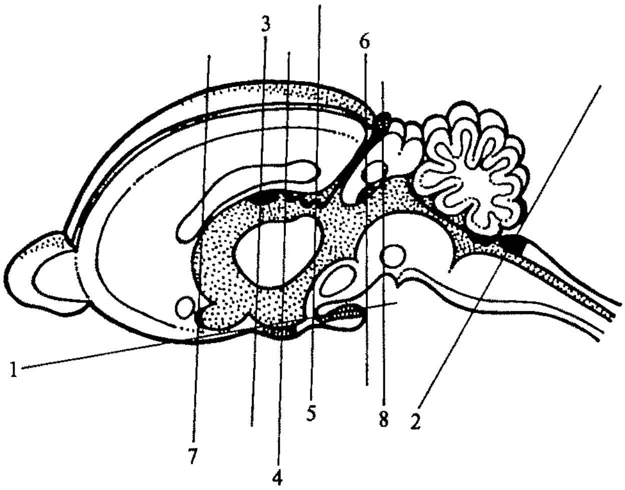

FIG. 1. Diagram of a sagittal section of the mouse brain showing the localization of the circumventricular organs and choroid plexus (cross-hatched regions). The orientation of sections used to obtain samples from these regions are also indicated. 1, neurohypophysis; 2, area postrema; 3, subfornical organ; 4, median eminence; 5, choroid plexus; 6, subcommissural organ; 7, prechiasmatic region; 8, pineal gland.

Light and electron microscopy

The examination was concentrated on two of the regions showing signs of epirubicin nuclear labelling, namely the pituitary gland and area postrema. Samples from these regions were examined both by light and electron microscopy, whereas the subfornical organ, the median eminence and the choroid plexus were investigated by light microscopy alone.

Pituitary gland. The mouse pituitary gland is composed of three concentric regions. The central portion, the neurohypophysis, is in continuity with the pituitary stalk, connecting the gland with the infundibular region of the brain. The intermediate lobe surrounds the neurohypophysis and separates that region from the ventrally and laterally situated adenohypophysis (Oota, 1963). The neurohypophysis of control mice contained a rich network of blood vessels with wide perivascular spaces. The extracellular space in other regions was very narrow. The pituicytes had a large, round nucleus and pale cytoplasm. Numerous axons containing secretory granules (secretory axons) were present, originating from the nerve cell bodies in the hypothalamus that innervate the neurohypophysis.

The mice injected with epirubicin surviving 7 and 13 days showed pronounced dilatation of the extracellular spaces (fig. 3). This enlargement increased with survival time (figs 4, 5) and, at 30 and 45 days after injection, the parenchyma showed a spongy appearance on light microscopy. The changes in the size of extracellular spaces seemed to develop simultaneously with cell changes. Alterations in the shape and staining quality of the parenchymal cells began at 7 days. At that stage pituicytes were pale and contained intracytoplasmic vacuoles. Their nucleus stained only faintly with toluidine blue and was displaced to the periphery.

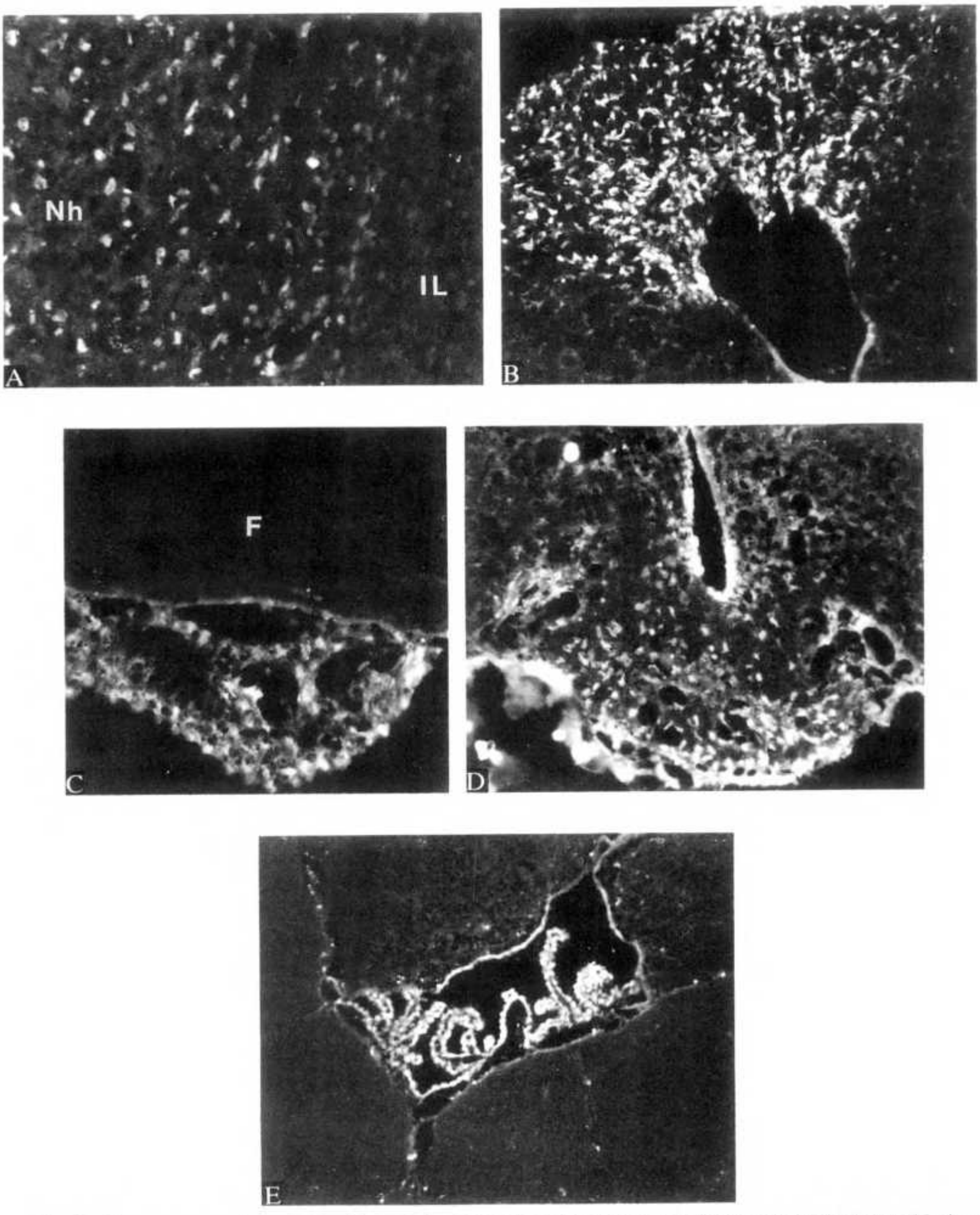

FIG. 2. Fluorescence micrographs of cryostat sections from the circumventricular organs and choroid plexus of a mouse given epirubicin intravenously 1 h before the removal of the samples. A, pituitary gland (plane 1, fig. 1). Epirubicin has leaked into the neurohypophysis and accumulated preferentially in the nuclei of the cells. Nh = neurohypophysis I.L. = intermediate lobe. ×290; B, area postrema (plane 2, fig. 1). There is extensive nuclear labelling in the area postrema whereas no specific fluorescence is present in the surrounding brain tissue. ×220. C, subfornical organ (plane 3, fig. 1), showing marked nuclear fluorescence in this region and the absence of fluorescence in the adjacent brain tissue. F = fornix. ×205. D, median eminence (plane 4, fig. 1) showing extensive extravasation and nuclear labelling. ×295. E, choroid plexus and tissue surrounding one lateral ventricle (plane 5, fig. 1), showing pronounced accumulation of fluorescent epirubicin in the epithelial cells of the plexus. ×110.

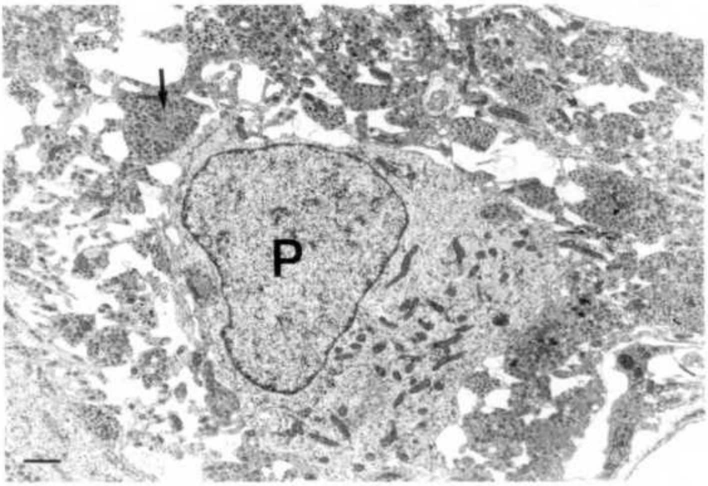

FIG. 3. Electron micrograph of the neurohypophysis from a mouse 13 days after an i.v. injection of epirubicin, showing large extracellular spaces (clear areas) between the axons and pituicytes (P). The axons from the hypothalamic nuclei can be identified by the presence of secretory granules (arrow). Bar = 1 μm.

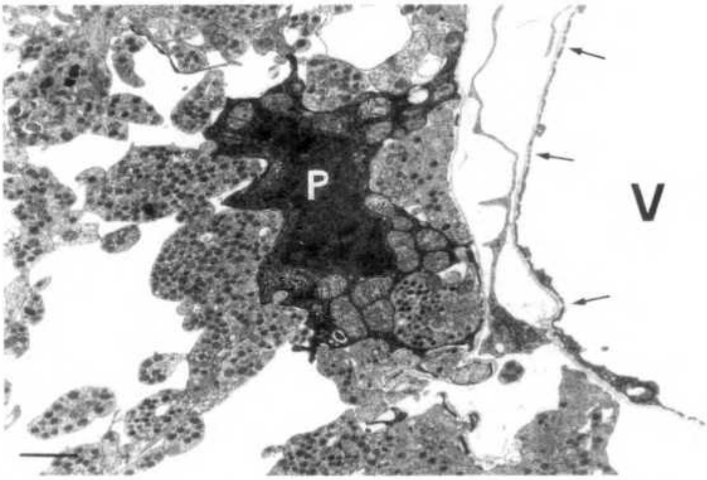

FIG. 4. Electron micrograph of the neurohypophysis from a mouse 30 days after an i.v. injection of epirubicin showing that the extracellular spaces are wider than those in fig. 3. There is one blood vessel (V) surrounded by very large spaces. The vascular endothelium contains several fenestrations (arrows). The centre of the figure is occupied by a degenerated, electron dense pituicyte (P). Bar = 1 μm.

The earliest cellular alterations seen by electron microscopy were confined to the nucleus and the nucleolus, with rarefaction of chromatin particles and nucleolar segregation and disintegration. Cytoplasmic changes, such as accumulations of dense bodies, neurofilaments and altered mitochondria, loss of ribosomes and polysomes, and pronounced vacuolation, followed the nuclear alterations. Mice with a survival period of 30 to 45 days had lost numerous pituicytes and the remaining ones were shrunken and darkly stained (figs 4, 5). The nucleus was pyknotic and the cytoplasm contained many vacuoles and altered mitochondria.

Electron microscopy showed that the parenchyma had a considerable number of markedly abnormal neurosecretory axons at 30 and 45 days survival. There were focal swellings of such axons which contained large accumulations of altered organelles including dense bodies, multilamellar figures, vesicles and multivesicular bodies (fig. 6). The swollen axons containing darkly stained material could easily be detected by light microscopy in toluidine blue stained sections.

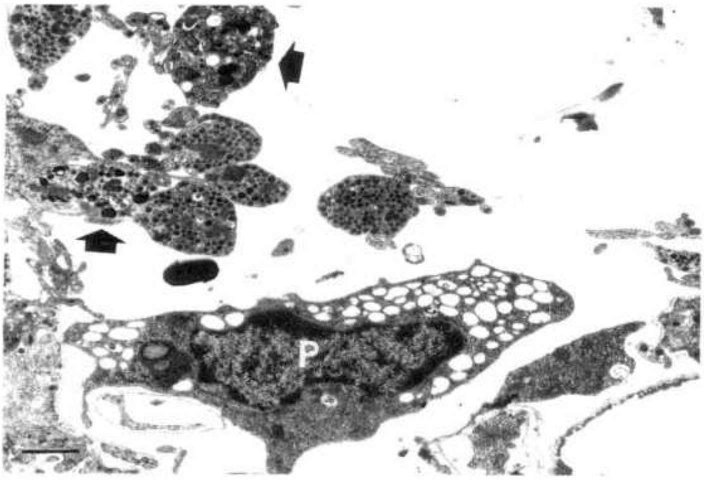

FIG. 5. Electron micrograph of the neurohypophysis from a mouse 45 days after an i.v. injection of epirubicin showing several axons containing secretory granules together with accumulations of dense bodies (arrows). Note the very large extracellular spaces and the vacuolated degenerated pituicyte (P). Bar = 1 μm.

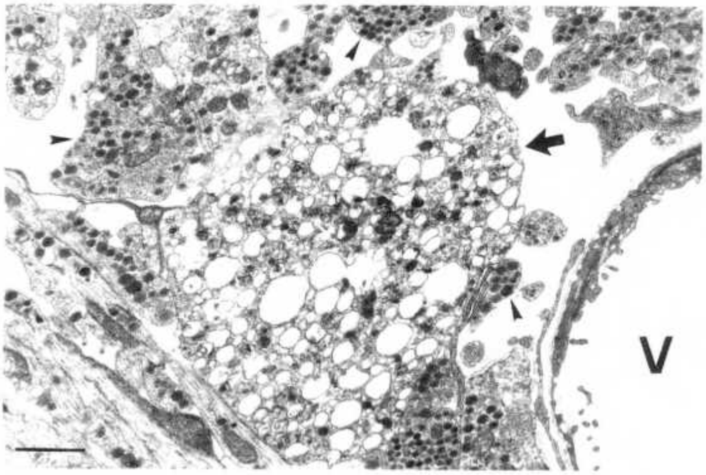

FIG. 6. Electron micrograph of the neurohypophysis from a mouse 30 days after an i.v. injection of epirubicin. A degenerating axonal swelling (arrow) contains many vacuoles, dense bodies and multilamellar figures. Normal axons (arrow heads) with dense secretory granules are also seen. V = blood vessel. Bar = 1 μm.

The intermediate lobe and adenohypophysis showed no morphological alterations.

Area postrema. The area postrema of control animals had a compact parenchyma formed by two types of cell: neurons with a large nucleus, light chromatin and a prominent nucleolus, and astrocyte-like cells, with dense chromatin, a central honeycombed nucleolus and dense cytoplasm. Many axons were present between the cells and the perivascular spaces were wide. The area postrema of mice surviving 7 and 13 days after the injection of epirubicin had a loose, somewhat spongy appearance. Some cells had a pale nucleus which was displaced peripherally. At 30 and 45 days of survival many cells were vacuolated and several shrunken, dark and degenerated cells were also present. Electron microscopy showed that these cells had cytoplasmic accumulations of altered mitochondria, dense bodies and dilated smooth endoplasmic reticulum.

Subfornical organ and median eminence. On light microscopy, the subfornical organ and the median eminence in mice given epirubicin and allowed to survive

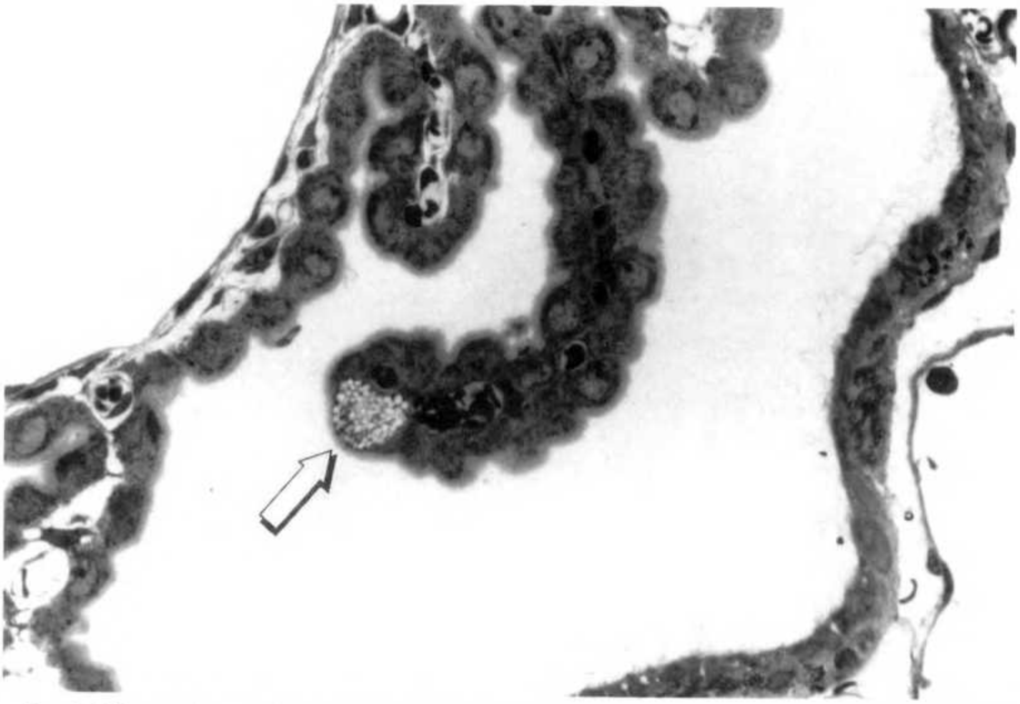

FIG. 7. Micrograph of semithin section of the choroid plexus from a mouse 30 days after an i.v. injection of epirubicin. A degenerating epithelial cell (arrow) shows pronounced cytoplasmic vacuolation. Toluidine blue, × 340.

for 7 or 13 days showed a loose appearance. Animals which survived for 30 or 45 days had a more dense structure. Vacuolated as well as shrunken degenerated cells were present.

Choroid plexus. The choroid plexus showed some vacuolated epithelial cells at 7 and 13 days survival. A few epithelial cells displayed an impressive vacuolation of their cytoplasm and pyknosis of the nucleus at 30 and 45 days (fig. 7). Most fibroblasts of the plexus were shrunken and darkly stained.

DISCUSSION

The mechanism of the cytotoxicity of the anthracycline compounds has been a matter of discussion and is not precisely known. However, most authors agree that the major action on cells is a direct effect on the chromosomal DNA due to an intercalation of the compounds into the DNA double helix with disruption of the nucleic acid strands. This interference with nucleic acids then has consequences for protein synthesis in the cells (Cho, 1977; Cho *et al.*, 1980; Jortner and Cho, 1980; Cavanagh *et al.*, 1987). Anthracyclines may also cause injury by effects on cell membranes, by interference with calcium and sodium regulation (Murphree *et al.*, 1976), by influences on intracellular electron transport (Olson *et al.*, 1974) and by generation of free radicals (Myers *et al.*, 1977; Olson *et al.*, 1981).

This fluorescence microscope study showed that detectable amounts of epirubicin do not cross the BBB and that after an i.v. injection the drug has access to all regions of the brain located outside the BBB (*see* Rapoport, 1976; Bradbury, 1979, 1985; van Deurs, 1980; Crone, 1986; Goldstein and Betz, 1986; Partridge, *et al.*, 1986). Our preliminary unpublished observations also indicate that it spreads into the ganglia of the peripheral nervous system in the same way as many other substances from the blood (*see* Olsson, 1984).

Epirubicin fluorescence was detected in cell nuclei of the choroid plexus and of all the circumventricular organs, except the subcommissural organ. Unlike those in the other circumventricular organs (*see* Sposito and Gross, 1987), the capillaries of the subcommissural organ are not fenestrated (Wetzstein *et al.*, 1963) and are impermeable to i.v. injected doxorubicin (Bigotte *et al.*, 1982*a*) and horseradish peroxidase (Weindl and Joynt, 1973).

The circumventricular organs are important regions since they have neuroendocrine and neuroreceptor activities (Weindl, 1973). The possibility that haemocirculating toxic agents may reach these areas and there cause cell injury is therefore of considerable interest. We have previously demonstrated that doxorubicin can produce cell lesions in some of the circumventricular organs (Bigotte and Olsson, 1983*a*). The present investigation shows that i.v. injected epirubicin exerts a cytotoxic action in the epithelium of the choroid plexus, the neurohypophysis, the median eminence, the area postrema and the subfornical organ. The functional implications of lesions in the circumventricular organs remain to be determined. A recent study quantitated the basal secretion of adrenocorticotrophic hormone, corticosterone and vasopressin in rats given a single i.v. injection of doxorubicin (Jezova *et al.*, 1986). Thirty days after the injection the plasma levels of these hormones showed no alterations and no changes in the concentrations of vasopressin were detected in the neurohypophysis, the median eminence and the hypothalamic nuclei. However, the possible impairment of pituitary hormone responses to appropriate stimulation has not been investigated.

Injection of epirubicin caused marked changes in the neurohypophysis. The number of altered neurons and abnormal secretory axons, as well as the intensity of the changes, increased with the survival time. Mice killed at 30 and 45 days after injection showed loss of cells and a large number of swollen axons. These altered axons correspond to the so-called type II Herring bodies which are considered to be hallmarks of degeneration in neurosecretory axons (Dellmann and Rodríguez, 1970; Dellmann, 1973). If the functional activities of pituicytes and of tanycytes of the median eminence are maintained, the degeneration of secretory axons is accompanied by phagocytic incorporation of axonal debris and lipid droplets, the so-called cellular 'activation' (Dellmann *et al.*, 1974; Rechardt and Hervonen, 1982). Degenerative axonal changes and signs of cell 'activation' are seen, for instance, in aged mice and following transection of the pituitary stalk (Dellmann and Owsley, 1969; Rechardt and Hervonen, 1982).

The cellular changes that we observed in the neurohypophysis and the median eminence do not correspond to cell 'activation'. The alterations seen in the cells of these regions as well as in the area postrema and the subfornical organ follow the temporal pattern observed when a toxic compound interferes with protein formation. Thus the earliest alterations were confined to the nucleus and the nucleolus, with rarefaction of chromatin particles and nucleolar segregation and disintegration. Cytoplasmic changes, such as accumulations of dense bodies, neurofilaments and altered mitochondria, loss of ribosomes and polysomes and pronounced vacuolation, followed the nuclear alterations. Such alterations have previously been observed as cytotoxic effects of doxorubicin in some of the circumventricular organs of the mouse (Bigotte and Olsson, 1983*a*) and in other types of brain cells, both in vivo and in vitro (Cho *et al.*, 1980; Eddy and Nathaniel, 1982; Bigotte and Olsson, 1984; Zagoren *et al.*, 1984).

The reason why axons in neurohypophysis and median eminence degenerate is not clear. The secretory axons which pass into these regions originate from neurons located in the hypothalamic nuclei and i.v. injected epirubicin did not leak across the vessels in these nuclei. The changes may, of course, be the result of a direct effect of the compound on the axolemma, in line with the knowledge that other anthracyclic drugs alter the permeability of membranes (Olson *et al.*, 1974; Murphree *et al.*, 1976). However, the possibility that axonal changes might be a consequence of primary injury to the neuronal perikaryon by retrograde transport of epirubicin deserves some consideration. The retrograde axonal transport of materials from the neurohypophysis and median eminence to the hypothalamic nuclei has been proposed for exogenous proteins such as horseradish peroxidase (Broadwell and Brightman, 1976). It should also be recalled that there are barriers preventing extracellular diffusion of molecules from the circumventricular organs into the brain (Krisch *et al.*, 1978; Bigotte *et al.*, 1982*a*). It is not yet known if epirubicin can be transported by retrograde axonal transport and the survival period up to 2 h used for fluorescent tracing of epirubicin in this study is too short to allow detectable amounts to reach the hypothalamus. However, the parent compound, doxorubicin, can be transported by retrograde axonal transport and then cause nerve cell degeneration both in motor and sensory systems (Bigotte and Olsson, 1983*b*; Yamamoto *et al.*, 1984; Van der Kooy *et al.*, 1985; Bigotte and Olsson, 1987; Kondo *et al.*, 1987). A similar mechanism might then be implicated in the production of epirubicin toxicity on the hypothalamic neurons, with consequent degeneration of their secretory axons in the neurohypophysis and the median eminence.

In conclusion, this investigation demonstrates that i.v. injected epirubicin is neurotoxic in the mouse and that its effects on the CNS are similar to those previously observed after administration of its analogue, doxorubicin.

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LATERAL VISUALLY-GUIDED SACCADES IN PROGRESSIVE SUPRANUCLEAR PALSY

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SUMMARY

Lateral visually-guided saccades were studied electro-oculographically in 40 patients with progressive supranuclear palsy (PSP) in order to increase understanding of the pathophysiology of the oculomotor syndrome and the suprareticular control of saccades. In the two main paradigms used, the central fixation point was removed just before the appearance of a lateral target, the subject being told either to look at the target (gap task) or, particularly to test frontal lobe influence, in the direction opposite to the target (antisaccade task). Saccade latency distribution in the gap task was significantly more scattered in patients as compared with 40 normal control subjects, although mean latencies did not differ greatly. In particular, many patients had latencies shorter or longer than those of control subjects. In the PSP group, the percentage of errors in the antisaccade task (misdirected saccades made towards the target) was strongly correlated with latency in the gap task, high percentages of errors corresponding to short latencies. There was also a correlation between latency and the frontal dysfunction evaluated by neuropsychological tests. These correlations suggest that short latencies could result from a severe impairment of the frontal inhibitory system involved in saccade initiation. Long latencies would result from damage to diverse excitatory suprareticular pathways (such as the superior colliculus) or to circuits responsible for shifts in visual attention. Lastly, 20 patients were followed longitudinally (for 3–12 months). The initially great intersubject variability of saccade latency in the gap task significantly decreased over a period of several months. This finding could result from a secondary balance between the impairment of the frontal inhibitory system and that of the diverse excitatory pathways.

INTRODUCTION

Progressive supranuclear palsy (PSP), described by Steele *et al.* (1964) includes a complex parkinsonian syndrome (*see* Agid *et al.*, 1986) and a characteristic oculomotor impairment, affecting saccades and smooth pursuit but sparing reflex vestibular movements. Disturbances of saccades usually occur early in the course of the disease, in the vertical and horizontal planes successively, and grow progressively worse over a few years up to paralysis (Troost and Daroff, 1977).

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The degenerative process essentially involves subcortical structures (Steele *et al.*, 1964; Steele, 1972; Dubas *et al.*, 1983; Kish *et al.*, 1985; Ruberg *et al.*, 1985), but the frontal cortex is also impaired, at least functionally (D'Antona *et al.*, 1985). The purpose of this study was to advance understanding of the pathophysiology of the oculomotor syndrome and the respective roles of the frontal lobe and subcortical structures in the control of saccades. Visually-guided saccades were analysed electro-oculographically in 40 patients with PSP and a longitudinal study was performed in 20 of them. Several paradigms were used, including an 'anti-saccade' task (Guitton *et al.*, 1985) to test more precisely the role of the frontal lobe on oculomotor control.

PATIENTS AND METHODS

Patients

Forty patients hospitalized in 9 different neurological departments of Paris hospitals between 1985 and 1988 were considered to have PSP on the basis of multiple clinical criteria proposed in several recent reports (Jackson *et al.*, 1983; Agid *et al.*, 1986; Maher and Lees, 1986). Each of them had all the following characteristics: (1) extrapyramidal axial rigidity (with facultative rigidity of the limbs), without tremor; (2) absence or poor response to levodopa treatment; (3) paralysis or evident slowness of vertical saccades always involving (but not necessarily predominantly) downward movement, with preservation of vertical oculocephalic movements; (4) unsteady gait with falls; (5) dysarthria, eventually associated with pseudobulbar palsy; (6) frontal lobe-like symptomatology; (7) gradual development of the disease; (8) normal CT scan, except for slight or moderate diffuse atrophy. These 8 points were required because they strongly supported the diagnosis of PSP. Two further points were also required for this study: (9) persistence of some voluntary lateral mobility of the eyes; and (10) absence of severe intellectual deterioration. Because of this last criterion, certain patients in the terminal stage of the disease were not included in the study.

Some of the main clinical characteristics of the 40 patients included are summarized in Table 1. Mean age was 68 yrs (SD = 6.8 yrs). Mean duration of disease was 2.8 yrs (SD = 1.2 yrs) from the first electro-oculographic recording. All the following signs were also observed at that date. The impairment of vertical saccades was scaled 1 when velocity was decreased, but still permitted the target to be reached with one or usually several hypometric saccades; scaled 2 when there was both a decrease of saccade velocity and a reduction of the final amplitude of the movement (namely less than to 30°); and scaled 3 when the eyes remained fixed on the midline during attempted saccades. Vertical gaze impairment always involved downward movement (*see* above), predominantly so in 19 patients, predominantly upwards in 7 patients, and was equal in both directions in 14 patients (with complete paralysis in 8 cases). Extrapyramidal axial rigidity, particularly involving the neck, was also required but the limbs were not always rigid. Evaluation of intellectual deterioration and frontal lobe dysfunction were performed according to the procedures described by Pillon *et al.* (1986). Intellectual deterioration was considered to be absent in 18 patients, slight in 18 and moderate in 4. Frontal lobe-like activity was assessed by several tests including the simplified version of the Wisconsin card-sorting test, verbal fluency, graphic series, behavioural abnormalities (imitation, prehension and utilization behaviour, inertia and indifference). A global frontal score was calculated and expressed as a percentage of the best value obtained in normal subjects.

A control group of 40 subjects (mean age 64 yrs; SD 10.4) was studied with the same paradigms as the patients. The control subjects had no history of neurological disorder and were normal on neurological examination.

TABLE 1. MAIN CLINICAL DATA

			Vertical gaze paralysis		*Rigidity*			
						Limbs		
Case	*Age (yrs)*	*Duration of disease (yrs)*	*Down*	*Up*	*Axial*	*R*	*L*	*Intellectual deterioration*
1	80	2	2	3	3	0	3	2
2	61	2	3	2	2	0	1	1
3	56	3	3	3	2	0	0	0
4	68	4	2	1	1	1	1	0
5	61	4	1	0	3	2	2	1
6	57	2	2	3	2	0	0	1
7	74	3	3	2	2	1	0	2
8	72	3	2	1	2	1	1	1
9	81	6	2	1	3	1	1	0
10	66	3	1	0	1	0	1	0
11	59	2	3	3	1	1	1	0
12	71	4	3	1	2	0	0	1
13	67	2	2	3	1	0	0	1
14	51	2	3	3	1	1	1	1
15	73	5	3	3	1	0	0	1
16	70	2	2	1	2	1	1	0
17	63	1	2	1	1	0	0	1
18	72	3	3	1	1	0	1	0
19	76	2	2	2	1	3	2	1
20	70	1	3	2	2	1	1	0
21	67	3	3	3	1	1	1	1
22	66	2	2	2	1	1	1	0
23	61	2	2	2	1	1	1	0
24	67	4	2	2	1	2	1	1
25	65	2	2	2	1	1	1	1
26	73	3	3	2	3	0	0	1
27	71	4	2	1	2	1	0	1
28	76	1	1	2	2	0	0	0
29	60	2	2	3	2	1	1	0
30	65	3	1	0	1	1	0	1
31	72	4	2	1	2	1	1	1
32	72	2	2	3	2	1	1	0
33	72	4	3	3	2	1	1	2
34	78	1	3	3	1	0	0	0
35	77	3	3	2	1	0	0	0
36	72	6	2	3	2	2	1	2
37	60	4	2	2	1	0	0	1
38	71	2	1	0	2	0	0	0
39	65	2	3	3	3	2	1	0
40	68	2	1	0	1	1	2	0

L = left; R = right. 0, 1, 2, 3 = no, slight, moderate and severe impairment, respectively. For vertical gaze, *see* text.

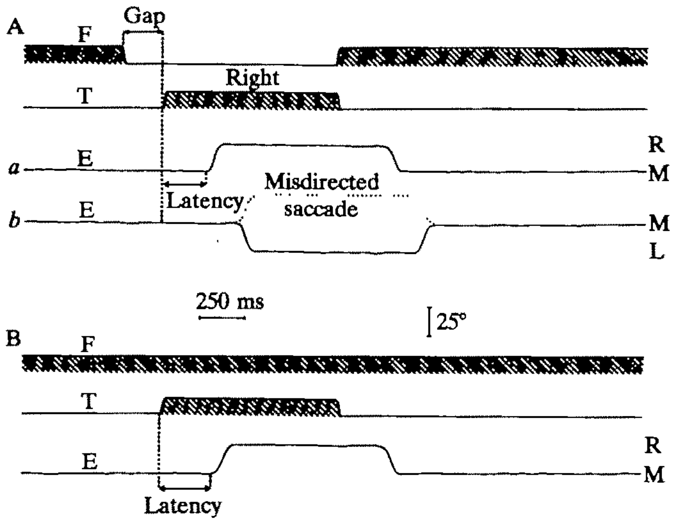

FIG. 1. Paradigms. A, with a gap of fixation (the central fixation point is turned off a little before the appearance of the lateral target). *a*, the gap task: the subject is told to look at the target; *b*, the antisaccade task: the subject is told to look in the opposite direction to the target. B, without gap of fixation (the central fixation point is permanently turned on): the overlap task, the subject being told to look at the target. E = eye (control subject); F = central fixation point; T = lateral target; L = left; R = right; M = midline.

Eye movement recordings

Eye movements were recorded by D.C. electro-oculography (EOG) in darkness with 4 electrodes (2 horizontal temporal and 2 vertical on one eye). The head was immobilized.

Lateral visually-guided saccades were studied with 3 paradigms. In the first (fig. 1A*a*), called the gap task, disappearance of the central fixation point was followed after a time interval (gap) by the appearance of a luminous lateral target located 25° to right or left of the central point. The subject was required to fix first the central point and then the lateral target as quickly as possible after its appearance. Right and left presentations were randomly alternated with unpredictable timing. Gap duration was also randomly varied between 100 and 300 ms (i.e., 200 ms on average). Right and left saccade latencies were calculated for each subject by averaging 30 measurements made in each lateral direction. These calculations excluded saccades with latency less than to 75 ms, probably corresponding to anticipatory movements (Fischer and Ramsperger, 1986), and those with latency greater than to 800 ms, probably resulting from inattention. In fact, these two types of saccades were rare both in patients and control subjects. In most patients, saccades were both slow and hypometric, and several small successive saccades were necessary to reach the 25° amplitude. In addition, asymmetry between right and left saccades was studied for each subject using the difference between the highest and lowest right or left latency. In 20 patients, the gap task was performed two or three times in the course of the disease.

In the second paradigm (fig. 1A*b*), called the antisaccade task, the same procedure (also with a gap of fixation) was performed, but the subject was told to look in the opposite direction to the suddenly-appearing lateral target, at its mirror location. The percentage of misdirected saccades (reaching the target or simply beginning in its direction) was determined in each lateral direction. This task was also repeated in the 20 patients longitudinally studied.

In the third paradigm (fig. 1B), called the overlap task, there was no gap of fixation. The central fixation point remained visible during the whole procedure which was otherwise the same as in the first paradigm. Right and left saccade latencies were quantified in the same way.

Statistical analysis

Comparisons of saccade latencies measured in different situations (PSP group vs control group, right vs left, gap vs overlap) were performed by variance analysis (F test). Further comparisons of two variances and of two means were made by the F test and t test, respectively. The paired t test was used to compare mean saccade latencies measured at successive times in the course of the disease. Since the percentage of misdirected saccades in the antisaccade task and the frontal score did not have a normal distribution, their correlations with saccade latency in the gap task were carried out using a nonparametric test (Spearman rank correlation coefficient).

Significance was accepted at the $P < 0.05$ level. Values given throughout the paper are mean ± SEM. The normal range of right and left saccade latencies in the gap task, defined as the mean value in the control group ± 2 SD is indicated in figs 2, 4 and 5 for the sake of clarity.

RESULTS

First examination

Individual data and mean results are summarized in Tables 2 and 3, respectively. In the gap task, mean latency of left saccades was only just significantly longer in the PSP group than in the control group ($P < 0.05$), while the difference in right mean latencies was not significant. However, variance comparisons indicated that latency variance was significantly higher in the PSP group than in control subjects, for right as well as left saccades ($P < 0.001$ for both). For individual data (fig. 2)

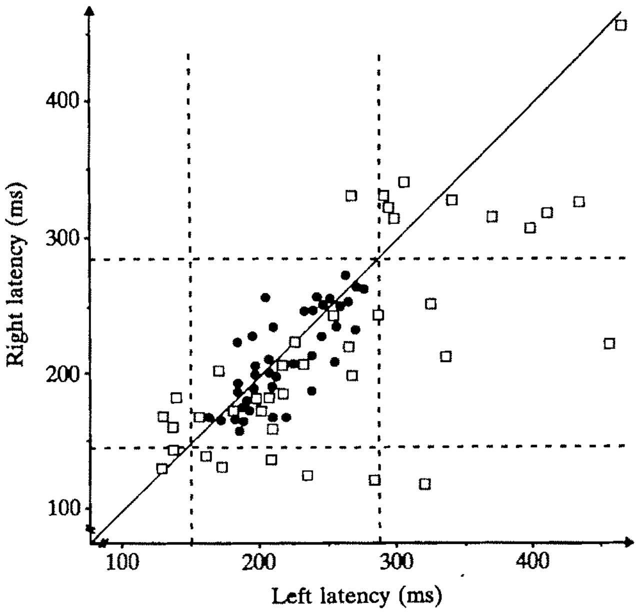

FIG. 2. Distribution of saccade latency in the gap task on first examination. The filled circles are the control subjects and the open squares the patients with PSP. Horizontal and vertical dashed lines indicate the limits of the normal ranges for right and left values, respectively. Note that values of patients were more asymmetric than those of control subjects, and also that many patients had latencies noticeably shorter or longer than control subjects.

TABLE 2. INDIVIDUAL RESULTS IN THE PSP GROUP (FIRST EXAMINATION)

	Gap task latency (ms)			*Overlap task latency (ms)*		*Antisaccade task errors (%)*		
Case	*Right*	*Left*	*Asymmetry*	*R*	*L*	*R*	*L*	*Frontal score* (%)
1	132	128	4	161	182	100	100	6
2	132	171	39	146	129	100	96	2
3	149	139	10	313	395	79	75	42
4	141	159	18	186	204	64	48	44
5	162	135	27	276	210	50	62	17
6	140	201	61	195	284	90	90	26
7	157	135	22	190	183	100	100	7
8	184	144	40	287	262	39	95	33
9	127	232	105	252	309	100	13	19
10	124	280	156	204	514	55	29	—
11	123	317	194	204	423	100	13	19
12	172	159	13	266	201	75	95	27
13	161	203	42	204	254	92	58	4
14	205	169	36	259	176	87	89	29
15	164	187	23	—	—	100	100	8
16	184	194	10	306	310	75	62	20
17	174	208	34	208	284	68	60	42
18	181	197	16	246	225	41	45	45
19	190	211	21	193	298	79	91	47
20	208	218	10	238	253	91	75	47
21	210	230	20	285	269	100	100	11
22	225	225	0	330	245	20	66	51
23	200	264	64	235	347	50	40	—
24	224	260	36	321	339	31	27	49
25	245	254	9	298	279	33	45	49
26	244	278	34	300	274	100	60	7
27	211	335	124	323	496	100	40	60
28	252	325	73	217	381	80	21	56
29	259	460	201	512	473	9	11	32
30	336	268	68	370	343	0	33	32
31	319	299	20	615	523	27	30	55
32	323	298	25	412	422	16	33	51
33	336	296	40	339	270	57	63	24
34	320	371	51	403	450	17	18	—
35	314	400	86	339	493	0	27	49
36	346	305	41	380	362	10	29	32
37	326	429	103	464	406	56	23	25
38	329	337	8	410	404	30	17	44
39	320	406	86	—	—	36	45	31
40	454	460	6	464	557	0	0	50

— = not tested.

TABLE 3. OVERALL RESULTS IN CONTROL GROUP AND PSP GROUP (FIRST EXAMINATION)

	Gap task latency (ms)			*Overlap task latency (ms)*		*Antisaccade task errors (%)*		
	R	*L*	*Asymmetry*	*R*	*L*	*R*	*L*	*Frontal score* (%)
Control group	214±5	218±5	19±2	226±10	222±8	16±3	15±3	92±2
PSP group	225±13	257±15	49±8	299±17	327±18	59±5	54±5	33±3

Values are mean±SEM.

the distribution of latencies was much more scattered in the PSP group than in control subjects; in particular, many patients had latencies shorter or longer than those of control subjects. Furthermore, fig. 2 shows that latency was more asymmetric in patients than in control subjects. This is confirmed by a significantly higher mean asymmetry of right and left saccade latencies in patients (49 ± 8 ms) than in control subjects (19 ± 2 ms, $P < 0.001$).

In the overlap task, mean saccade latencies of patients were significantly longer than in the gap task ($P < 0.001$, for right as well as left). By contrast, in control subjects, the difference in mean latencies between the overlap task and the gap task was not significant.

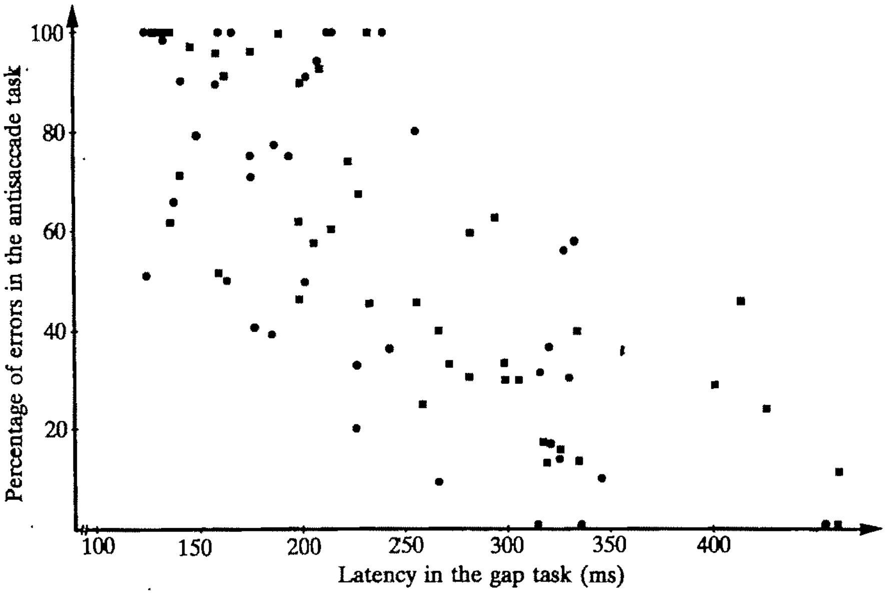

FIG. 3. Graph of saccades latency in the gap task vs errors in the antisaccade task. The circles are the right values and the squares the left values of the 40 patients with PSP.

In the PSP group, the percentage of errors (misdirected saccades) in one direction in the antisaccade task was highly correlated with the latency of saccades performed in the same direction in the gap task (fig. 3): $r = -0.824$ ($P < 10^{-9}$) and $r = -0.657$ ($P < 10^{-7}$) for left and right, respectively. The shorter the saccade latency in the gap task, the higher the percentage of errors in the antisaccade task. This correlation could not be demonstrated in the control group.

Significant correlations were also found in the PSP group between the frontal score and saccade latency in the gap task: $r = 0.439$ ($P < 0.01$) and $r = 0.471$ ($P < 0.01$) for left and right, respectively. The shorter the saccade latency in the gap task, the more marked the frontal dysfunction. Accordingly, these results show that at a relatively early stage of the disease patients with short latencies in the gap task usually had severe frontal dysfunction, making numerous errors in the antisaccade task, while those with long latencies had only slight or moderate frontal dysfunction, making only a few errors in the antisaccade task.

Longitudinal study

In 20 patients latency of visually-guided saccades in the gap task was measured two or three times in the course of the disease. Results were collected in 3 groups, corresponding to first examination, second examination between 3 and 9 months later (6 months on average), and third examination 1 yr after the first.

TABLE 4. EVOLUTION OF GAP TASK SACCADE LATENCY IN PSP GROUP

	Right latency (ms)	*Left latency (ms)*
First examination	223±16	268±21
Second examination	200±10	240±13
Third examination	244±27	295±30

Values are mean±SEM.

Between the first and the second examination, mean latencies of right and left saccades showed a tendency to decrease, but this was not statistically significant (Table 4). However, almost all the patients who had the longest or the shortest saccade latencies in the first examination had, 3 to 9 months later, latencies much more closely grouped around the mean latency in the normal group (fig. 4). These decreases in the latency variances were significant for right and left saccades ($P < 0.02$ for both).

By contrast, fig. 5 shows that right and left saccade latencies increased from the

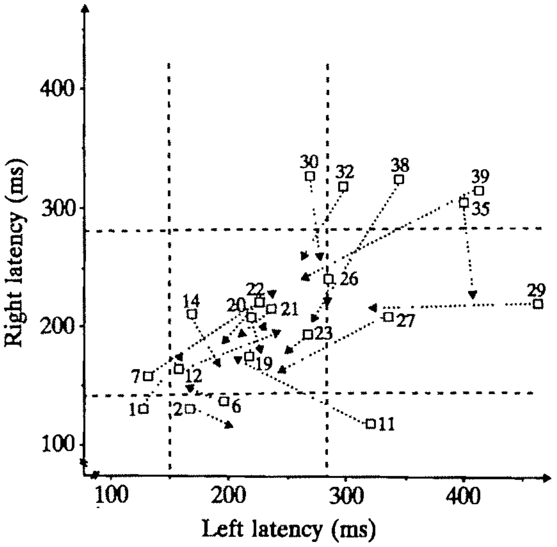

FIG. 4. Evolution of latencies between first and second examinations. The squares are latencies on first examination (with the numbers of patients), and the arrows are latencies on second examination. Horizontal and vertical dashed lines indicate the normal ranges for right and left values, respectively. Note that latencies were much less scattered on the second examination, most of the shortest and longest latencies having moved towards the normal mean.

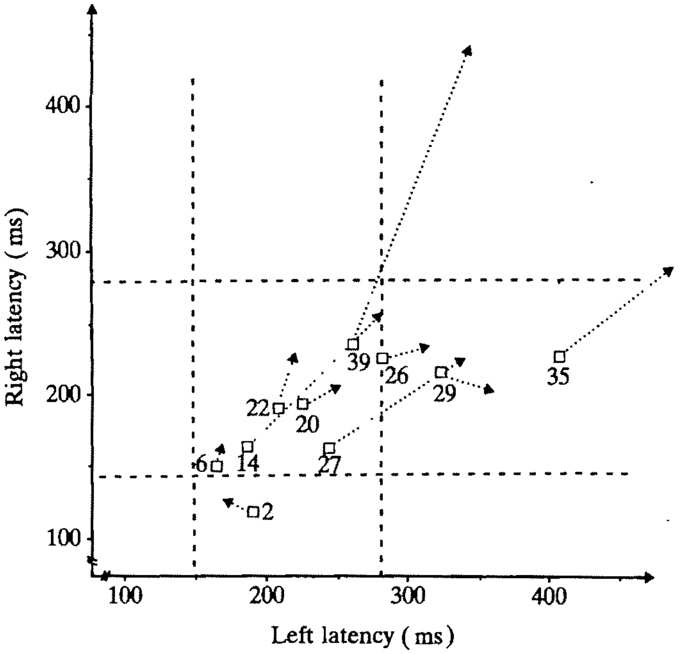

FIG. 5. Evolution of latencies between the second and third examinations. Squares are latencies on the second examination (with the numbers of patients), and arrows are latencies on third examination. Horizontal and vertical dashed lines indicate the normal ranges for right and left values, respectively. Note that most values had increased at the third examination.

second to the third examination, 1 yr after the first examination. It should be noted that, at the third examination, the different correlations described above (between latency in the gap task and either percentage of errors in the antisaccade task or the frontal score) were no longer found. In particular, long saccade latency in the gap task was combined in certain patients with a high percentage of errors in the antisaccade task as well as with a low frontal score.

DISCUSSION

A review of the supranuclear organization of saccades and of the location of damage in PSP is necessary for an interpretation of these results. The paramedian pontine reticular formation (PPRF) lying in the pontine tegmentum is the premotor relay of all ipsilateral saccades (fig. 6) (Leigh and Zee, 1983; Pierrot-Deseilligny, 1985; Hanson *et al.*, 1986). Saccade velocity depends on the paramedian pontine reticular formation (PPRF), but also significantly on certain suprareticular structures (Tusa *et al.*, 1986; Pierrot-Deseilligny *et al.*, 1988). Initiation of saccades could be controlled by two excitatory tracts, arising from the superior colliculus (SC) and the frontal eye fields (FEF), respectively, and projecting directly onto the PPRF (for review, *see* Tusa *et al.*, 1986). Thus experimental bilateral lesions

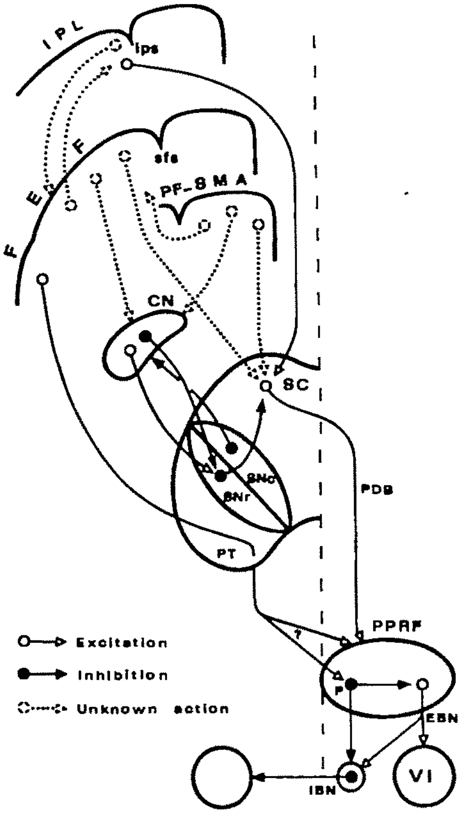

FIG. 6. Hypothetical organization of supranuclear pathways of lateral visually-guided saccades. CN = caudate nucleus; EBN = excitatory burst neurons; FEF = frontal eye fields; IBN = inhibitory burst neurons; IPL = inferior parietal lobule; ips = intraparietal sulcus; P = pause neurons; PDB = predorsal bundle; PF = prefrontal cortex; PPRF = paramedian pontine reticular formation; PT = pyramidal tract; SC = superior colliculus; SMA = supplementary motor area; SNc = substantia nigra, pars compacta; SNr = substantia nigra, pars reticulata; sfs = superior frontal sulcus; VI = abducens nucleus; ? = the termination of the frontoreticular tracts is not yet known.

of the FEF alone or of the SC alone result in subtle and temporary deficits of saccades while bilateral lesions of both structures lead to a severe and long-lasting deficit of saccades (Schiller *et al.*, 1980). The excitatory frontal and collicular pathways could, therefore, act complementarily in the triggering of visually-guided saccades and supplant each other in case of lesions.

The SC is essentially a relay on to which several cortical efferent tracts project. Some of them arise directly from the FEF but also from the prefrontal cortex and the supplementary motor area (SMA), located anteriorly and medially to the FEF, respectively (DeVito and Smith, 1959; Leichnetz *et al.*, 1981; Komatsu and Suzuki, 1985; Goldman-Rakic, 1987; Segraves and Goldberg, 1987). The SMA is involved in spontaneous and visually-guided saccades in simple as well as in complex oculomotor tasks (Melamed and Larsen, 1979; Fox *et al.*, 1985; Schlag and Schlag-Rey, 1987). In fact, the respective roles of the SMA, of the prefrontal cortex, and of the direct frontocollicular tract arising from the FEF are not as yet well understood. On the other hand, it now appears probable that the parietocollicular tract, arising from the posterior part of the intraparietal sulcus and also projecting directly onto the SC, has an excitatory action in the triggering of visually-guided saccades (for review, *see* Pierrot-Deseilligny *et al.*, 1986, 1987).

Besides the pathways which play an excitatory role in the triggering of visually-guided saccades, there are other tracts whose final action is inhibitory. Such an inhibition is necessary to prevent, during foveal tasks for example, wasteful saccades on peripheral visual targets. The cortical area involved could be the dorsal part of the frontal lobe as well as the prefrontal cortex, since focal lesions involving these regions result at times in a latency decrease of certain visually-guided saccades essentially in the gap task or in the antisaccade task (Guitton *et al.*, 1985; Pierrot-Deseilligny *et al.*, 1987). These results have led to the proposition that the frontal lobe probably has a predominantly inhibitory action in the triggering of such visually-guided saccades. The course and the relays of the efferent frontal inhibitory pathways are not as yet well understood. Some of them could project directly onto the reticular formations of the brainstem or onto the SC (*see* above), or could have a relay in the pars reticulata of the substantia nigra (SNr). This structure contains inhibitory (GABAergic) neurons projecting onto the SC (Hikosaka and Wurtz, 1983, 1985, 1986). Their tonic activity ceases just before visually-guided saccades. This activity also ceases with the introduction of a simple new visual event, such as the disappearance of the central fixation point or the occurrence of a peripheral target, especially if there is a gap between the two events (Hikosaka and Wurtz, 1983). It has recently been shown that such a gap (included between 100 and 250 ms) facilitates the triggering of express saccades (with latency less than 140 ms) (Fischer and Breitmeyer, 1987; Mayfranck *et al.*, 1987). This facilitation in a gap task could result from a decrease of the SNr activity occurring just before the onset of the lateral target, because of the preliminary offset of the central fixation point. It should also be noted that certain direct frontocollicular neurons, active during foveal fixation, could be inhibitory (Segràves and Goldberg, 1987) and, therefore, involved in such a mechanism. One of the main afferences of the SNr is the striatum (Carpenter and Sutin, 1983), in particular the caudate nucleus, which contains inhibitory neurons active just prior to saccades, but otherwise silent (Hikosaka and Sakamoto, 1986). The caudate nucleus and the putamen could also contain excitatory neurons (with substance P as neurotransmitter) projecting onto the SNr (Carpenter and Sutin, 1983; Beckstead, 1987). As the action of the frontocaudate tracts has not yet been investigated, the exact origin and course of the frontal inhibitory pathway(s) are still uncertain.

In PSP, the cerebral cortex is spared, excepting the frontal area in which some slight anatomical changes are at times found in postmortem studies (Steele *et al.*, 1964; Kish *et al.*, 1985; Ruberg *et al.*, 1985). These changes are not sufficient to explain the severe prefrontal dysfunction evidenced by diverse neuropsychological investigations in previous studies (Albert *et al.*, 1974; Cambier *et al.*, 1985; Pillon *et al.*, 1986) as well as in our patients. On the other hand, a clear hypometabolism of the frontal cortex detected by positron emission tomography (PET) may account for such a dysfunction (D'Antona *et al.*, 1985). It has been proposed that this frontal impairment would essentially be due to a deafferentation resulting from the subcortical lesions. The essential anatomical lesions are indeed located in subcortical structures, including the substantia nigra—the pars compacta much more than the pars reticulata—and the SC (Steele *et al.*, 1964). However, the pars compacta of the substantia nigra (SNc) is almost always severely damaged and the SC is at times slightly impaired (Steele *et al.*, 1964; Ishino *et al.*, 1975; Dubas *et al.*, 1983; Kish *et al.*, 1985; Ruberg *et al.*, 1985). The paramedian reticular formations of the brainstem are also damaged, more severely in the midbrain than in the pons. This probably explains why vertical and lateral saccades have a progressive decrease of velocity, preceding complete supranuclear paralysis, and why the vertical paralysis usually occurs earlier. Lastly, other anatomical structures—such as the pallidum, the subthalamic nucleus, the brachium conjunctivum, the pontine nuclei, the locus coeruleus and the dentate nuclei—are involved in the degenerative process, but it has not been shown so far that they play a role in saccade initiation.

Latency on first examination

In the gap task, latencies were significantly more asymmetric in the PSP group than in the control group. In nonhemianopic patients with unilateral cerebral hemisphere lesions, asymmetry of latencies of lateral visually-guided saccades was due to damage to the frontal subcortical white matter, probably containing the efferences from the oculomotor areas (Pierrot-Deseilligny *et al.*, 1987). The fact that the white matter of the hemispheres is spared in PSP (Steele *et al.*, 1964) strongly suggests that the asymmetry of latencies here was due to asymmetrical damage to structures onto (or towards) which these frontal efferences project, namely the substantia nigra, the superior colliculus and the PPRF (*see* below).

The distribution of individual latencies in the gap task was significantly more scattered in the PSP group than in the control group, with latencies shorter or longer in many patients. As discussed below, it may be suggested that short latencies and long latencies resulted from different anatomical and functional impairments: a predominant impairment of the inhibitory pathways or of the excitatory pathways involved in saccade initiation could create an imbalance in triggering control, leading to a decrease or an increase in latency.

Short latency. In certain patients, latency was near to or below 140 ms on average (Table 2). In each of these patients, therefore, many or most saccades, depending on the patients, were express saccades (Fischer and Ramsperger, 1984, 1986). Express saccades would require the integrity of the SC (Boch and Fischer, 1986; Schiller *et al.*, 1987). This is plausible, at least at an early stage of the disease, since, as previously mentioned, the SC is at times only slightly affected in postmortem studies of PSP. However, short latencies also suggested that the frontal inhibitory system could be impaired. This inhibitory system could influence both PPRF, by a direct tract, and the SC, via several relays (*see* above). The caudate nucleus is not affected or is only moderately affected in PSP (Steele *et al.*, 1964; Dubas *et al.*, 1983; Ruberg *et al.*, 1985), although a functional impairment cannot be excluded at this level. Although a lesion of the SNr could also exist and explain a decrease of latency, this mechanism does not appear, at least at the present time, to be the most probable for several reasons: (1) this structure is often largely spared in anatomical studies of PSP (Steele *et al.*, 1964; Dubas *et al.*, 1983); (2) although the GABAergic activity of the SNr has not been specifically studied, the GABAergic activity has been normal in PSP in almost all the subcortical structures in which it has been evaluated so far (Kish *et al.*, 1985; Agid *et al.*, 1986); (3) the existence here of latencies significantly shorter in the gap task than in the overlap task suggests the persistence of a functional role of the SNr, through which information of the disappearance of the central fixation point could be mediated (*see* above).

If the nigral relay of the frontal inhibitory pathways is not severely damaged, the frontal cortex itself could be impaired. This hypothesis is supported by several arguments. First, the cortical frontal lesions may induce a decrease of latency of visually-guided saccades in the gap task (Pierrot-Deseilligny *et al.*, 1987) and a severe functional impairment of this lobe has been reported in PSP (D'Antona *et al.*, 1985). Secondly, the disturbances of the antisaccade task, testing the functions of the frontal cortex (Guitton *et al.*, 1985) and perhaps more specifically of the prefrontal cortex (Goldman-Rakic, 1987; C. Pierrot-Deseilligny, unpublished data), were strongly correlated here with latency, such disturbances being at a maximum when latency was short. It may therefore be inferred that the frontal oculomotor areas were probably severely impaired in this instance. Thirdly, there was also a correlation between the shortness of latency and the severity of frontal dysfunction evaluated by the neuropsychological tests. Although these investigations test only the functions of the prefrontal cortex, they could provide an indirect indication on the condition of the close dorsal oculomotor cortex if the whole frontal cortex was affected by a functional impairment. Accordingly, it may be assumed that the decrease of latency was due to a dysfunction of the frontal cortex and/or of the underlying striatal structures.

Long latency. Latency was particularly long in certain patients. Correlations with the antisaccade task and with neuropsychological tests first indicate that the frontal cortex was probably much less impaired in these patients than in those with short latency. These results suggest that the condition of the frontal cortex could in fact be the main factor influencing latency in the initial period of the disease. In the absence of severe damage to the frontal cortex, namely to the inhibitory system, a certain impairment of the excitatory subcortical pathways involved in saccade initiation could then become apparent by the increase of the latency. Such an increase could theoretically result from damage to the PPRF, the SC or the substantia nigra. Lesions of the PPRF affect velocity of saccades (Hanson *et al.*, 1986), but it is not yet known whether such lesions also influence latency. The SC is more or less damaged in PSP and an anatomical lesion (Heywood and Ratcliff, 1975; Wurtz and Goldberg, 1972; Albano *et al.*, 1982) or a chemical inactivation (Hikosaka and Wurtz, 1985, 1986) of this structure results in an increase of latency. Damage to the SNc could also be involved here. An increase of latency has indeed been reported in Parkinson's disease as well as in intoxication with MPTP, in which damage essentially involves the SNc (Shibasaki *et al.*, 1979; Fisk *et al.*, 1982; White *et al.*, 1983; Bronstein and Kennard, 1985; Hotson *et al.*, 1986). As the SNc projects onto the caudate nucleus which in turn projects onto the SNr (Carpenter and Sutin, 1983), damage to this nigro-caudo-nigral pathway could be involved in latency increase. Unlike subjects intoxicated with MPTP (Brooks *et al.*, 1986; Hoston *et al.*, 1986) levodopa therapy did not influence latency in patients with PSP (C. Pierrot-Deseilligny, unpublished data), perhaps because, with this disease, there is in addition a loss of the striatal dopamine receptors (Baron *et al.*, 1985; Ruberg *et al.*, 1985). Accordingly, it may be proposed that long latencies in our patients possibly resulted from damage to the SC and/or to the SNc. However, an alternative hypothesis exists to explain this increase of latency. It could also result from damage to circuits responsible for shifts in visual attention, since it may be that such circuits are impaired in PSP (Posner *et al.*, 1982).

Longitudinal study

The rapidity of the course of the disease as well as the time at which the oculomotor disturbances occur are rather variable from one patient to another. However, besides their diagnostic interest, the different inclusion criteria used here, particularly the prior presence of vertical gaze disorders as well as the absence of severe intellectual deterioration, led to the examination of patients at roughly similar time points in relation to the course of the disease. Intersubject variability of saccade latencies in the gap task significantly decreased between the first and the second examination (several months later), with a clear tendency for longest and shortest latencies to return towards normal in spite of the worsening of the disease. This worsening was marked in particular by the progressive diminution of saccade velocity throughout the course of the disease. In a few cases, velocity could even be near zero while latency was still short. Lastly, latency had a clear tendency to increase between the second and the third examinations, a few latencies being very long at this late stage of the disease.

The mechanisms which accounted for latencies remaining normal, or for their normalization between the first and the second examinations while the disease worsened, can be deduced from the previous discussion concerning short and long latencies. In each case, it was suggested that certain anatomical structures controlling latency in one way were initially more impaired than other structures controlling latency in the other way. If these two types of structures were similarly impaired, this would be sufficient to preserve or to re-equilibrate latency from the beginning of the disease or at a subsequent stage of its course. It must be noted, however, that at a late stage of the disease latency sometimes increased again while the percentage of errors in the antisaccade task was also high and the frontal score very low. In addition to damage to the frontal inhibitory system, severe damage both to the frontal excitatory system and to the collicular excitatory pathway could explain this late increase of latency. As in the experiments of Schiller *et al.* (1980) in the monkey, no possibility of compensation in the different excitatory pathways would then exist which could trigger saccades.

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CNV ABNORMALITIES FOLLOWING CLOSED HEAD INJURY

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SUMMARY

Event-related potentials (ERPs) were recorded in a GO/NO-GO reaction time task from 20 closed head injury patients, at least 6 months postinjury, and from 20 controls. In this task the pitch of an initial tone (S1) indicated whether or not a response was required to a second tone (S2) occurring 1.5 s later. In the control group both the early, frontal-maximum, and the later vertex-maximum, components of the contingent negative variation (CNV) were larger on GO than NO-GO trials. In the patients, the early frontal CNV wave did not differentiate GO and NO-GO trials, and the late CNV showed a smaller separation between these trial types than did the late CNV of the control group. These CNV abnormalities may reflect impairments in selectively orienting to salient stimuli, and in differential response preparation. Such impairments might in turn reflect the damage to the frontal lobes and/or their connections that commonly occurs as a result of closed head injury.

INTRODUCTION

Although the deleterious effects of closed head injury on a wide range of psychological functions are well known (Levin *et al.*, 1982; Brooks, 1984), relatively little work has investigated indices of cerebral activity, such as event-related brain potentials (ERPs), during the performance of cognitive tasks by head-injured patients. We (Rugg *et al.*, 1988) have previously outlined the reasons why ERPs might be a useful means of studying the effects of head injury. Briefly, (1) ERPs are sensitive to a number of important cognitive variables; (2) they give a relatively direct real-time record of some of the neural events accompanying task performance; and (3) the scalp distribution of ERP abnormalities may allow the formulation of hypotheses about abnormally functioning brain regions.

In our previous paper (Rugg *et al.*, 1988), we reported ERP data from an auditory 'oddball' task, in which subjects were required silently to count low probability 'target' tones interspersed among high probability nontargets. Although their counts were as accurate as those of the controls, closed head injury

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patients showed, relative to the control group, enhanced amplitudes and delayed latencies in the 'N2' ERP component evoked by the target tones. We interpreted this finding as indicating a deficit in these patients in the efficiency of early perceptual categorization processes, evident even in a task as simple as the oddball procedure.

In the present paper, we describe ERPs recorded from closed head injury patients and control subjects during performance of a GO/NO-GO reaction time (RT) task, allowing the study of ERP activity associated with prestimulus as well as poststimulus processing. In this task, which was first employed with closed head injury patients by Curry (1980, 1983), the first of a pair of stimuli (S1) signals whether or not a response is required to a second stimulus (S2) occurring 1.5 s later. The GO/NO-GO task is a modification of the forewarned simple RT paradigm used in many studies to investigate the contingent negative variation (CNV; Walter *et al.*, 1964). The CNV is a sustained negative-going ERP wave occurring during the interval between S1 and S2 in paradigms such as forewarned RT. It was originally interpreted as a single ERP component, associated with anticipatory or expectancy processes. It is now clear that the CNV consists of at least two overlapping negative-going components, an earlier one evoked by S1, and a later component preceding but associated with S2 (Rohrbaugh and Gaillard, 1983). The first of these components, which is maximal over frontal scalp areas, appears to be a response to S1, and to reflect some process akin to orienting (Loveless, 1979; Rohrbaugh, 1984). The second component has been identified with the so-called 'readiness potential', a slow ramp-like negativity that precedes spontaneous movements (Kornhuber and Deecke, 1965). Whether the CNV consists also of other components, reflecting nonmotor anticipatory processes contingent on the relationship between S1 and S2, is controversial (Rohrbaugh *et al.*, 1986).

When elicited in a GO/NO-GO paradigm, both the early and late components of the CNV are enhanced on GO trials in normal subjects (Curry, 1983, 1984). The GO/NO-GO difference in the early component presumably reflects the greater salience attributed to stimuli signalling the need for response preparation, whereas the difference in the late component reflects the fact that motor preparation is only required on GO trials. Curry (1983) reported that when tested some months after injury, patients who had suffered moderate or severe closed head injuries showed smaller differences between GO and NO-GO trials than controls, both in early and late measures of the CNV. He also reported, as have others (Rizzo *et al.*, 1978), that the CNV was smaller in patients than controls. These results suggest that closed head injury patients may be impaired in the use of information which allows differential response selection, and may also suffer an impairment in some aspect of response preparation itself.

In the present study, we sought to replicate and extend Curry's results by determining whether our sample of head-injured patients also showed abnormalities in the CNV in a GO/NO-GO task. We have also addressed the issue of how such abnormalities might be interpreted: do they directly reflect localized brain dysfunction common to most head-injured patients, or instead result from strategies adopted to compensate for slowness in information processing, and thus only indirectly reflect the underlying neuropathology?

METHODS

Subjects

Twenty patients (2 female) were employed. All had suffered a closed head injury at least 6 months before testing and fulfilled one or more of the following criteria: (1) Glasgow Coma Scale on admission to hospital of 8 or lower; (2) presence of an intracerebral haematoma; (3) posttraumatic amnesia (PTA) greater than 48 h. The characteristics of the patient group are summarized in Tables 1 and 2. Table 2 also describes the control group, which consisted of 20 subjects (all male). All of these had been admitted to an accident and emergency unit as a result of trauma, excluding the head, at least 6 months before testing. None had any known history of head injury.

The patients showed the typical sequelae of closed head injury. Of the 4 WAIS subtests employed, the patients were relatively unimpaired on the vocabulary task, but performed poorly on the others, and were particularly disadvantaged on the digit-symbol subtest. The patients also performed

TABLE 1. CHARACTERISTICS OF EACH MEMBER OF THE PATIENT GROUP

				WAIS						*Rey*				
	Age	*EDU*	*PTA*	*V*	*S*	*D*	*O*	*WMS*	*B*	*C*	*R*	*RT*	*WI*	*FR*
1	30	12	1	7	8	6	12	12.5	94	36.0	32.0	488	13	N
2	27	13	1	8	7	2	9	19.5	95	28.0	15.5	—	8	N
3	23	12	1	7	8	7	10	8.0	124	36.0	32.0	579	5	Y
4	28	18	1	10	10	7	12	11.5	66	36.0	19.0	495	11	N
5	19	12	2	8	7	4	13	8.5	80	36.0	18.5	536	—	Y
6	25	12	2	9	9	9	14	13.0	116	30.0	23.0	484	7	N
7	16	12	2	12	10	7	7	21.0	118	36.0	20.0	404	5	N
8	19	12	2	10	9	7	13	17.0	113	36.0	24.0	479	25	Y
9	24	12	2	7	6	8	13	11.0	94	32.0	22.0	372	9	N
10	38	13	2	8	6	6	11	14.0	73	30.0	13.0	560	12	Y
11	39	11	2	9	7	6	10	6.0	43	33.0	12.0	674	8	N
12	24	20	2	16	14	12	15	19.0	113	36.0	30.0	464	—	N
13	50	12	2	8	6	6	10	10.5	39	36.0	28.0	722	12	Y
14	22	12	2	7	7	6	9	5.5	72	34.0	10.5	669	11	Y
15	26	12	3	13	10	6	11	16.5	90	34.0	23.0	577	12	N
16	19	12	3	8	6	5	10	9.0	61	34.0	22.5	543	6	Y
17	28	12	3	11	10	3	12	12.5	112	32.0	16.5	766	23	Y
18	34	14	3	11	8	7	9	18.0	98	35.0	13.0	503	13	N
19	16	12	3	9	11	6	10	17.5	110	36.0	28.0	556	16	N
20	28	12	3	9	10	6	18	19.0	119	34.0	33.0	469	12	Y

Age (yrs); EDU = years of full-time education; PTA = length of posttraumatic amnesia (1 = 2 to 7 days, 2 = 8 to 14 days, 3 = 15 to 28 days); WAIS = age-scaled scores of vocabulary (V), similarities (S), digit-symbol substitution (D), and object assembly (O) subtests; WMS = summed associate learning score of Wechsler Memory Scale; B = long-term retrieval score on Buschke Selective Reminding Test; Rey = copy (C) and recall (R) performance on Rey figure; RT = Mean reaction time (ms) on four-choice RT task; WI = number of perseverative errors on Wisconsin Card Sorting Test; FR = presence (Y) or absence (N) of frontal pathology on CT scans.

TABLE 2. SUMMARY DATA FOR PATIENTS AND CONTROLS (SDs IN BRACKETS)

	Patients	*Controls*
Age (yrs)	26.7	26.8
	(8.45)	(9.31)
Years of full-time education	12.8	13.1
	(2.47)	(2.21)
WAIS (age-scaled scores)		
Vocabulary	9.35	10.65
	(2.32)	(2.66)
Similarities	8.45	10.10 $P < 0.05$
	(2.09)	(2.79)
Object Assembly	11.40	13.50
	(2.50)	(3.94)
Digit Symbol	6.30	10.20 $P < 0.001$
	(2.08)	(3.04)
Wechsler Associate Learning (sum)	13.48	16.28 $P < 0.05$
	(4.74)	(2.12)
Buschke Selective Reminding	91.5	115.1 $P < 0.01$
	(25.6)	(13.8)
Rey Figure Copy	34.0	34.58
	(2.45)	(2.11)
Rey Figure Recall	21.45	25.45
	(6.73)	(6.78)
Four-choice RT (ms)	544.1	436.2 $P < 0.001$
	(103.5)	(44.07)
Wisconsin Card Sorting (perseverative errors)	11.6	7.8 $P < 0.05$
	(5.5)	(3.7)

poorly as a group on two tests of verbal memory (Paired Associates test of the Wechsler Memory Scale and Buschke Selective Reminding Test), and were slower than the controls on a self-paced choice reaction-time task (4-choice RT; van Zomeren and Deelman, 1976).

EEG recording

EEG was recorded from 11 scalp sites, situated over the midline (Fz, Cz, Pz) and homotopic regions of the left and right hemispheres (75% of the distance from Fz to F7 (left frontal) and to F8 (right frontal), C3 and C4 (left and right central), T3 and T4 (left and right temporal), and P3 and P4 (left and right parietal). All EEG channels were referred to linked mastoids in the first 8 patients and controls tested, and to a noncephalic reference (Stephenson and Gibbs, 1951) thereafter. The change of reference was prompted by a concern to achieve maximum sensitivity for the detection of ERP asymmetries. One additional patient was subsequently tested using linked mastoids because of excessive ECG artefact from the noncephalic reference. EOG was recorded from a bipolar electrode pair situated above the right eye and on the outer canthus of the left eye. EEG and EOG were recorded with a bandwidth of 0.03–32 Hz (3 dB points), and sampled at a rate of 10 ms per point.

Stimuli and task

The stimuli consisted of tone bursts (80 dB SL, 50 ms duration, 10 ms rise and fall time) presented binaurally through headphones. Each trial consisted of the presentation of two tones (S1 and S2), separated by 1500 ms. S2 always had a frequency of 500 Hz. The frequency of S1 was either 250 or 750 Hz, and these frequencies occurred pseudorandomly across trials. Subjects were required to make a prompt motor response to S2, by depressing a switch with the thumb of the preferred hand, only on those trials on which S1 was of the 250 Hz frequency (GO trials). In the experimental run, 100 trials (50 GO, and 50 NO-GO) were presented, with an interval between the S2 of one trial and the S1 of the succeeding one of 7 s. A rest break was always given after the first 50 trials, and more frequently if necessary.

Subjects performed the task seated upright. They were instructed to avoid blinking or making body movements as much as possible, but especially during the interval from S1 until a second or so after S2. The importance of not responding on GO trials until they heard the second tone was emphasized. Twenty practice trials were given before the experimental run, and these were repeated if necessary until the subject complied with the task instructions.

Responses on NO-GO trials were logged as errors. Responses on GO trials with a latency less than 90 ms or greater than 1200 ms were also scored as errors, as were GO trials on which no response was made.

ERP recording

ERPs associated with GO and NO-GO trials were obtained by on-line averaging of each channel, including the EOG. Trials on which EOG activity exceeded a predetermined criterion, or on which response errors occurred (either of commission or omission) were automatically rejected from the averages.

RESULTS

ERPs

Grand average ERP waveforms are shown for the control and patient groups in fig. 1, and midfrontal and midcentral GO and NO-GO waveforms from each member of the two groups are overlaid in fig. 2. This figure shows that the variability of the waveforms in the two groups is comparable. A number of subjects could not suppress eye movements in response to S2, which caused a stimulus-locked EOG artefact in their post-S2 ERPs. For this reason, only the pre-S2 waveforms were subjected to analysis.

The grand averages of the control group show the expected pattern of CNV effects. GO and NO-GO S1 stimuli elicit initial N1 and P2 deflections following which the GO and NO-GO waveforms diverge, particularly at frontal and central scalp sites. In the GO waveforms, a frontal negative wave (the 'early' CNV) is followed by a sustained negativity, which remains at a fairly constant amplitude for the rest of the S1-S2 interval at Fz, but increases in amplitude over this interval at Cz and Pz. The NO-GO waveforms also elicit a frontal negative wave, but of smaller amplitude than in the GO condition. Following this wave, the NO-GO waveforms return to baseline. There is a slight tendency for the whole of the GO waveform, from approximately 300 ms post-S1 onwards, to be more negative-going at the left compared to the right central region. The patients' waveforms also exhibit a biphasic CNV after the N1 and P2 components. However, the frontal negative wave shows little difference between GO and NO-GO conditions, and the later regions of the wave show a smaller separation between GO and NO-GO trials than in the control data.

The ERP data were quantified by measuring the mean amplitude of selected

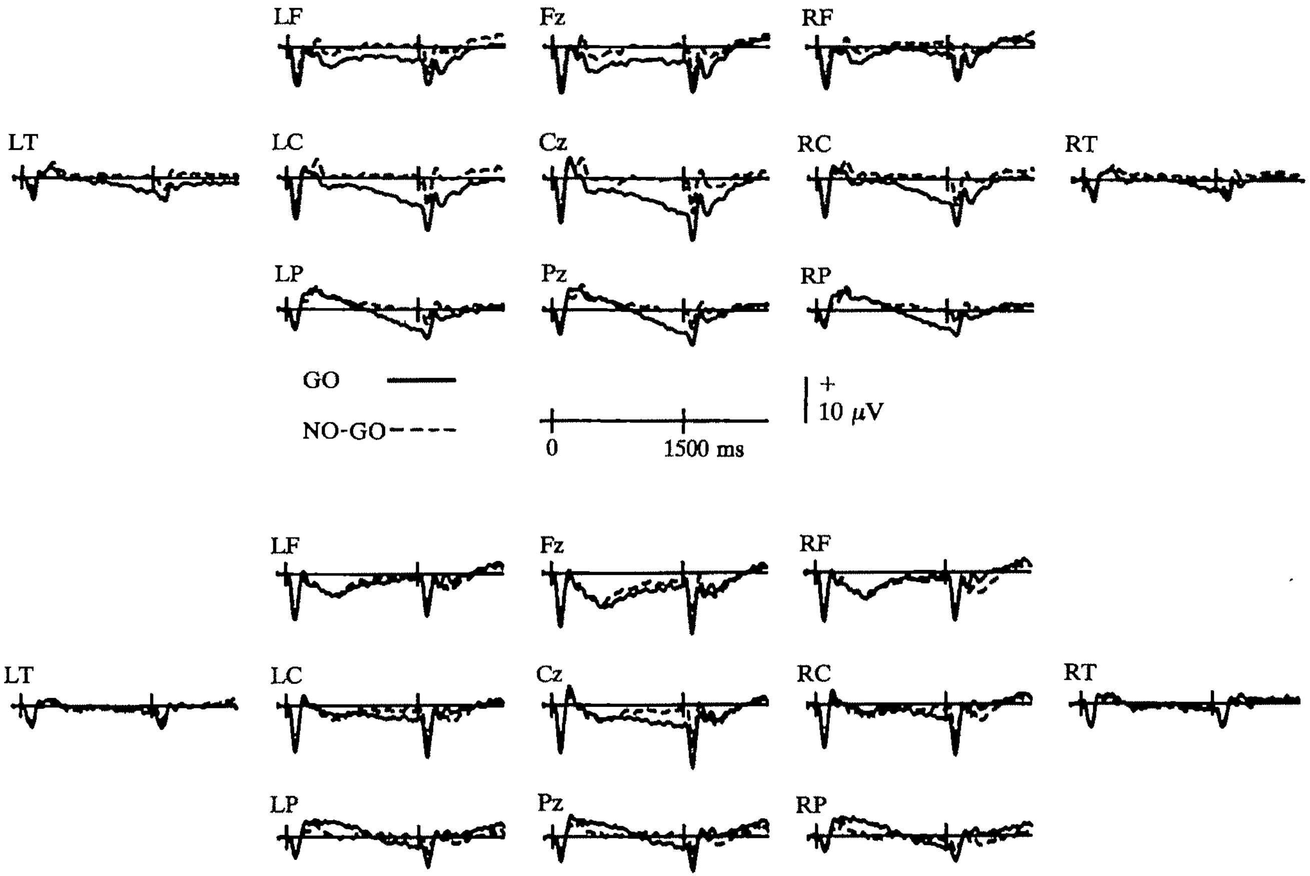

FIG. 1. Grand average GO and NO-GO waveforms of the controls (*upper half* of figure) and patients (*lower half*) from all electrode sites. (The data for the controls are based on only 19 of the 20 subjects; *see* p. 495 for explanation.)

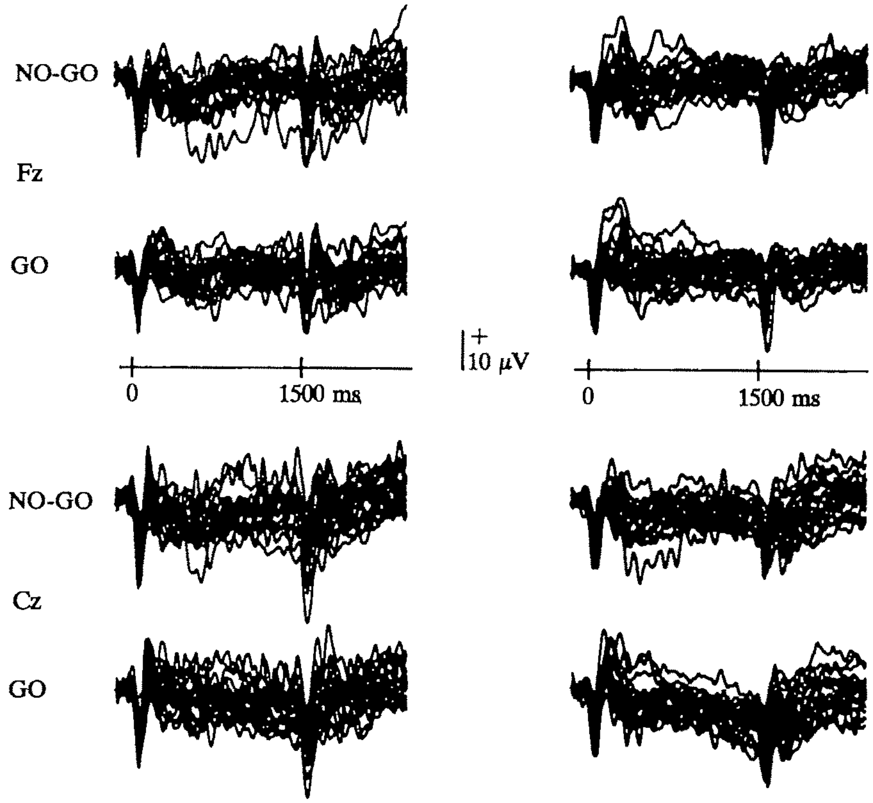

FIG. 2. ERPs from Fz and Cz electrodes of each member of the patient (*left column*) and control (*right column*) groups, overlaid separately for GO and NO-GO conditions.

regions of the waveforms. The early CNV was assessed by measuring the mean amplitude, with respect to the mean of the 100 ms pre-S1 baseline, of the 300–600 ms latency region, and the late CNV was quantified by measuring the mean amplitude, with respect to the same baseline, of the 1200–1500 ms region. These measurements were obtained with a computer program which determined the amplitude of the individual sampling points within a defined latency window, and then computed the arithmetic mean of these values. Two analyses were carried out on each measure, the first on data from the three midline electrodes, and the second on the data from lateral frontal, central and parietal sites. Because of an undetected technical problem, data from the right parietal electrode of 1 control subject were lost. In the analyses of the lateral sites, this missing data point was replaced by the mean of the remaining 19 controls. The analyses reported below were performed using three-way ANOVAs, with the between-subjects factor of group (patients vs controls), and the within-subjects factors of condition (GO vs NO-GO), hemisphere (in the case of the analyses of the lateral sites), and electrode site. All F ratios associated with repeated-measures factors were assessed using degrees of freedom corrected with the Greenhouse-Geisser procedure for controlling Type I error; corrected degrees of freedom are quoted when appropriate. Preliminary analyses, incorporating the additional factor of reference site (mastoids vs noncephalic), gave rise to effects which were qualitatively the same as those reported below.

TABLE 3. MEAN AMPLITUDE (AND SD) OF THE 300-600 ms LATENCY REGION OF THE NO-GO AND GO WAVEFORMS FROM THE PATIENT AND CONTROL GROUPS

	Fz	*Cz*	*Pz*	*LF*	*LC*	*LP*	*RF*	*RC*	*RP*
Patient									
NO-GO	−5.2	−2.2	1.7	−3.9	−1.9	1.6	−3.7	−1.5	1.5
	(3.5)	(3.6)	(3.3)	(3.4)	(3.0)	(3.2)	(4.1)	(3.8)	(3.7)
GO	−5.5	−1.9	3.5	−3.8	−1.4	3.8	−4.1	−0.7	3.9
	(3.3)	(4.0)	(5.1)	(3.4)	(4.1)	(5.2)	(3.7)	(3.8)	(4.9)
Control									
NO-GO	−0.9	1.3	3.7	−0.5	1.5	3.6	0.1	2.0	3.5*
	(4.4)	(4.7)	(4.1)	(3.9)	(4.4)	(3.7)	(3.6)	(3.9)	(3.7)
GO	−4.9	−2.2	3.0	−3.7	−1.4	3.3	−3.0	−0.5	3.3*
	(4.6)	(4.9)	(3.6)	(4.4)	(4.4)	(3.5)	(4.1)	(3.8)	(2.9)

* n = 19.

The 300–600 ms data are shown in Table 3. Analysis of these data from the three midline sites gave rise to a significant main effect of electrode site, (F1.4, 54.1 = 163.98, $P<0.001$), reflecting the anterior-posterior gradient in this region of the waveforms. Electrode site interacted with condition (F1.5, 58.8 = 21.75, $P<0.001$), reflecting the frontal maximum of the enhanced negativity occurring on GO trials. Finally, there was a significant interaction between group and condition (F1, 38 = 8.44, $P<0.01$). A posteriori analysis (Tukey's HSD) indicated that while the difference between GO and NO-GO conditions, averaged over electrodes, was reliable for the control group ($P<0.01$), this was far from significant for the patients, whose data showed a tendency to be more negative-going in the NO-GO condition. Tukey tests also showed that the data from the two groups differed in the NO-GO ($P<0.05$) but not the GO conditions.

Analysis of the 300–600 ms data from the lateral sites gave rise to a significant site effect (F1.4, 52.0 = 148.94, $P<0.001$), and to interactions between group and condition (F1, 38 = 9.68, $P<0.005$) and condition and site (F1.4, 52.0 = 22.16, $P<0.001$). The site effect reflected a tendency for this region of the waveform to be more negative-going at frontal electrodes. The group by condition interaction indicated, as for the midline data, that the GO/NO-GO difference was greater in the controls than the patients. A posteriori analysis of the data collapsed across electrodes revealed a significant GO/NO-GO effect only for the controls ($P<0.01$), and a significant group effect only for the NO-GO condition ($P<0.05$). The interaction between condition and site reflected the fact that, collapsed over groups, GO waveforms at frontal electrodes were more negative-going than NO-GO waveforms, while at parietal sites these differences tended to reverse.

The mean amplitudes of the 1200–1500 ms latency region are shown in Table 4. Analysis of these data from the midline sites revealed significant main effects of site (F1.6, 60.6 = 15.91, $P<0.001$) and condition (F1, 38 = 32.83, $P<0.001$). In addition the interactions between group and site (F1.6, 60.6 = 7.70, $P<0.005$), group and condition (F1, 38 = 4.64, $P<0.05$), and condition and site (F1.6, 62.0 = 13.37, $P<0.001$) were also significant. The first of these interactions reflects a tendency for the patients' waveforms, in both conditions, to be more negative frontally, and more positive parietally, than those of the controls. The interaction between group and condition indicates, as for the 300-600 ms data, that the controls yielded larger GO/NO-GO differences than the patients. However, in contrast to the 300–600 ms region, a posteriori analysis indicated that the GO/NO-GO difference, averaged across electrode sites, was significant both in the case of controls ($P<0.01$) and patients ($P<0.05$). The interaction between condition and site reflected the Cz maximum, in both groups, of the GO/NO-GO differences.

TABLE 4. MEAN AMPLITUDE (AND SD) OF THE 1200-1500 ms LATENCY REGION OF THE NO-GO AND GO WAVEFORMS FROM THE PATIENT AND CONTROL GROUPS

	Fz	*Cz*	*Pz*	*LF*	*LC*	*LP*	*RF*	*RC*	*RP*
Patient									
NO-GO	−2.1	−1.3	0.3	−1.0	−1.2	0.3	−1.7	−1.2	−0.3
	(4.1)	(3.6)	(3.6)	(3.8)	(3.7)	(4.6)	(4.3)	(3.6)	(5.2)
GO	−3.4	−4.8	−2.2	−1.3	−3.2	−1.9	−1.6	−3.0	−2.3
	(4.5)	(4.8)	(4.3)	(4.0)	(4.9)	(4.6)	(4.3)	(3.8)	(3.2)
Control									
NO-GO	0.5	−0.1	0.2	0.7	0.7	0.4	1.1	0.6	0.3*
	(3.1)	(3.2)	(3.2)	(3.2)	(2.9)	(2.6)	(3.0)	(3.0)	(3.1)
GO	−3.6	−7.3	−4.5	−3.1	−5.6	−3.9	−1.5	−4.5	−3.3*
	(3.2)	(3.8)	(2.9)	(2.9)	(3.4)	(2.8)	(3.7)	(3.2)	(2.5)

* n = 19.

Analysis of the 1200–1500 ms data from the lateral sites gave rise to significant effects of condition (F1, 38 = 20.36, $P<0.001$) and site (F1.4, 52.0 = 7.38, $P = 0.005$). In addition, there were significant interactions between group and condition (F1, 38 = 5.42, $P<0.025$), group and hemisphere (F1, 38 = 5.98, $P<0.025$), and condition and site (F1.4, 53.6 = 11.80, $P<0.001$). The condition by site interaction reflected the central maximum of the GO/NO-GO differences in this region of the waveform. The interaction between group and hemisphere was caused by a tendency for the waveforms, collapsed over site and condition, to be slightly more negative over the right hemisphere of the patients, but more negative over the left hemisphere of the controls. Finally, the group by condition interaction reflected larger GO/NO-GO differences in the controls' waveforms. A posteriori tests showed that these differences were reliable in the case of the control group ($P<0.01$), but not in the data from the patients.

Fig. 4 shows that 4 of the patients (11, 15, 16, 19) form an outlying group characterized by particularly poor performance on the task. To determine the extent to which the differences between patients and controls revealed by the foregoing analyses were influenced by these 4 poor performers, all the analyses were repeated after excluding their data (the unequal sizes of the groups were dealt with in the ANOVAs by the method of unweighted means). For the 300-600 ms CNV measure, the group by condition interactions were still reliable (midline sites: F1, 34 = 6.60, $P<0.02$; lateral sites: F1, 34 = 7.39, $P = 0.01$). However, the same interactions in the analyses of the 1200-1500 ms data were only of marginal significance (midline sites: F1, 34 = 2.91, $P<0.1$; lateral sites: F1, 34 = 3.41, $P<0.075$). To assess whether this reduction in the reliability of the differences between the groups reflected an association in the patients between task accuracy and the size of GO/NO-GO differences in the late CNV, a correlation was computed between response accuracy and the GO/NO-GO difference measured at Cz, the site where this difference was largest. This correlation was not significant ($r_{18} = 0.342$), suggesting that the effects of removing the 4 poorly performing patients resulted merely from a reduction in the statistical power of the group contrast.

The foregoing analyses do not allow an assessment of whether the ERPs of patients and controls differed in degree of ERP asymmetry independently of the direction of such asymmetries. This was determined by analysing the absolute differences in amplitude between homotopic pairs of electrodes. These data are shown for the 300-600 and 1200-1500 ms intervals in Table 5. ANOVA of the 300-600 ms data revealed significant effects of group (F1, 38 = 7.97, $P<0.01$) and electrode site (F1.4, 51.3 = 4.29, $P<0.05$), and a significant interaction between

TABLE 5. MEAN (AND SD) OF ABSOLUTE INTERHEMISPHERIC ASYMMETRIES (μV) BETWEEN FRONTAL, CENTRAL AND PARIETAL LATERAL ELECTRODES FOR GO AND NO-GO WAVEFORMS IN THE 300-600 AND 1200-1500 ms LATENCY RANGES

	300-600			*1200-1500*		
	Fron.	*Cen.*	*Par.*	*Fron.*	*Cen.*	*Par.*
Patient						
NO-GO	3.0	1.9	1.4	1.8	1.3	1.6
	(3.0)	(1.9)	(1.5)	(1.6)	(1.9)	(1.8)
GO	2.1	2.0	1.9	2.3	2.0	1.6
	(2.9)	(2.7)	(2.4)	(2.9)	(2.7)	(2.1)
Control						
NO-GO	1.7	1.2	1.6	0.9	0.7	0.7
	(2.0)	(1.7)	(0.9)	(1.1)	(0.9)	(1.0)
GO	1.4	1.4	1.0	2.8	1.7	1.0
	(1.7)	(1.6)	(1.4)	(3.2)	(1.7)	(1.5)

electrode site and condition (F2.0, 74.7 = 3.40, $P<0.05$). These effects reflected the larger size of the patients' interhemispheric asymmetries in this latency range, and the fact that averaged across the groups, asymmetries tended to be largest between frontal sites in the NO-GO condition. Analysis of the 1200–1500 ms data did not give rise to any effects involving the factor of group, but did reveal significant effects for condition (F1, 38 = 13.92, $P = 0.001$) and electrode site (F1.6, 59.9 = 9.48, $P = 0.001$), and for the interaction between these two factors (F1.9, 73.4 = 3.90, $P<0.05$). These effects reflected the larger asymmetries that occurred in the GO compared to the NO-GO waveforms, particularly between frontal electrodes. The nature of the reference (i.e., mastoids vs noncephalic) had no influence on the size of the asymmetries for the patients or controls at either latency interval.

In summary, the patients' CNVs showed smaller differences between GO and NO-GO conditions than did the controls'. In the case of the early CNV, the patients' GO and NO-GO waveforms were of a comparable magnitude to one another, and to the GO waveforms from the controls. The late CNV in the patients discriminated between the conditions at midline sites, but the magnitude of this condition effect was significantly smaller than that shown by the controls. These effects can be seen in fig. 3, which plots early and late GO/NO-GO differences for each subject.

TABLE 6. MEAN N1 (AND SD) LATENCY (ms) AND AMPLITUDE (μV) FOR NO-GO AND GO WAVEFORMS FROM THE PATIENT AND CONTROL GROUPS

	Latency			*Amplitude*		
	Fz	*Cz*	*Pz*	*Fz*	*Cz*	*Pz*
Patient						
NO-GO	111.8	111.2	109.0	−11.5	−10.4	−6.1
	(13.8)	(11.2)	(15.4)	(4.0)	(3.5)	(2.7)
GO	118.8	115.3	112.5	−13.0	−11.8	−6.8
	(15.2)	(12.8)	(18.6)	(4.5)	(4.1)	(3.7)
Control						
NO-GO	108.0	103.0	98.0	−9.7	−9.5	−5.9
	(17.0)	(14.8)	(15.2)	(4.2)	(4.2)	(3.0)
GO	116.5	115.0	105.0	−12.0	−11.7	−6.8
	(17.3)	(13.6)	(15.5)	(4.0)	(4.0)	(3.0)

In addition to the foregoing CNV analyses, the peak latency and amplitude of the N1 component was measured at midline sites; these data are shown in Table 6. ANOVA of the latencies revealed significant effects for condition (F1, 38 = 15.73, $P<0.001$) and site (F1.3, 50.3 = 5.92, $P<0.025$). These effects reflected shorter N1 latencies in the NO-GO condition and at the Pz electrode. No effects involving the factor of group were reliable. ANOVA of the amplitudes gave rise

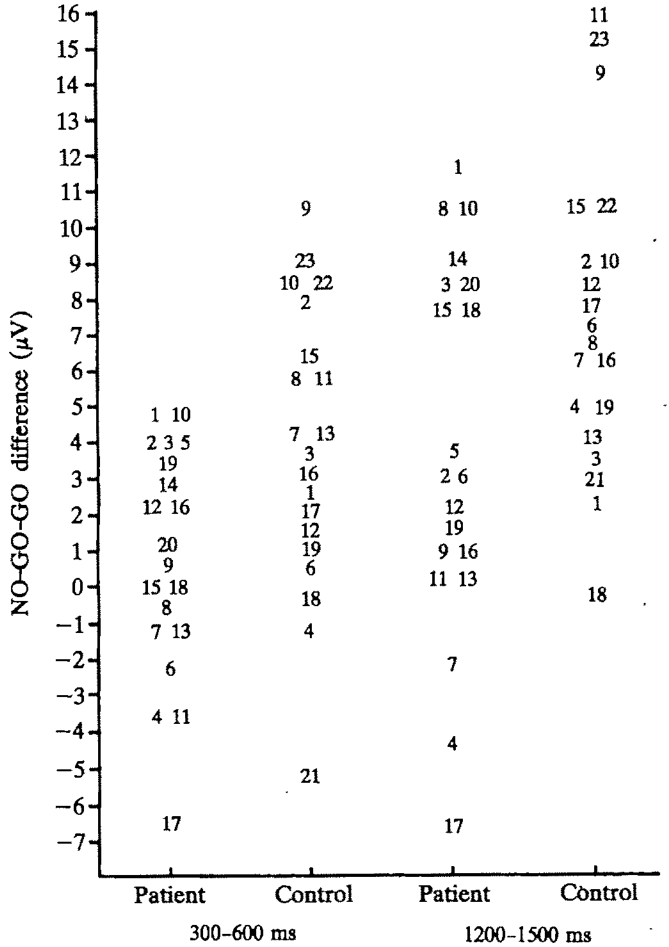

FIG. 3. GO/NO-GO differences for each member of the control and patient groups, as measured at Fz for the 300-600 ms latency region, and at Cz for the 1200-1500 ms region. Members of each group are identified by number, and patients belonging to each of three categories of posttraumatic amnesia duration are identified (7 days or less, 1–4; 8–14 days, 5–14; 15–28 days, 15–20).

to a significant GO/NO-GO effect (F1, 38 = 9.12, $P = 0.005$), and an interaction of this factor with electrode site (F1.4, 54.8 = 9.05, $P = 0.001$). These effects were due to N1 being of larger amplitude, particularly at Fz and Cz, when elicited by GO stimuli. All effects involving the factor of group were associated with F ratios of less than 1.

Task performance

Mean RT on GO trials, and accuracy of response choice, are shown in Table 7. An overall measure of accuracy was computed for each subject by using an adjusted measure of correct responding, which took account of the number of

TABLE 7. MEAN RT (ms) OF RESPONSES ON GO TRIALS, AND PERCENTAGE OF GO (CORRECT) AND NO-GO (INCORRECT) TRIALS, ON WHICH RESPONSES WERE MADE, FOR PATIENT AND CONTROL GROUPS

	RT	*Correct*	*Incorrect*
Patient	395.4 (211.3)	77.2 (20.1)	0.6 (0.8)
Control	354.2 (208.5)	91.2 (10.6)	0.1 (0.4)

'guesses' within this response category by applying the formula % correct = 100 × [(% responses on GO trials − % responses on NO-GO trials)/(100 − % responses on NO-GO trials)]. These data are plotted for each subject, along with RT, in fig. 4. This figure shows that the accuracy data are highly skewed, with 3 control subjects at ceiling. A Mann-Whitney test indicated that the patients' median accuracy score was significantly lower than the controls ($P<0.01$). When the 4 patients (11, 15, 16, 19) forming an outlying group were removed from the analysis, this difference failed to achieve significance ($P<0.1$). A t test showed that the difference between the mean RTs of the two groups was not significant.

Relationship between CNV and behavioural measures

In view of previous findings of an association between the amplitude of the terminal CNV and RT (Rohrbaugh and Gaillard, 1983), the 1200–1500 ms measure of subjects' GO waveforms was correlated with their RTs. The correlation coefficient across patients was 0.137, which was far from significant, and dropping the 4 patients (8, 9, 12, 17) who formed an outlying group of poor performers did not markedly increase its value ($r = 0.243$). In the controls, however, the analogous correlation was 0.502 ($df = 18$, $P<0.025$), indicating that more negative-going CNVs were associated with faster responses. When the 2 outlying control subjects (1, 3) were dropped, on the grounds that they could be causing a spurious association, the correlation rose to 0.578 ($df = 16$, $P<0.025$).

Relationship with severity of injury

Severity of injury was assessed by length of posttraumatic amnesia (PTA), and the patients were categorized according to the scheme of Brooks (1976). The patients falling into each severity category are shown in Table 1 and figs 3 and 4. It can be seen that there is little relationship between this measure of severity of injury and either behavioural or electrophysiological measures in the GO/NO-GO task.

DISCUSSION

The results of this study clearly demonstrate abnormalities in head-injured patients' ERPs recorded in the GO/NO-GO paradigm, confirming a previous

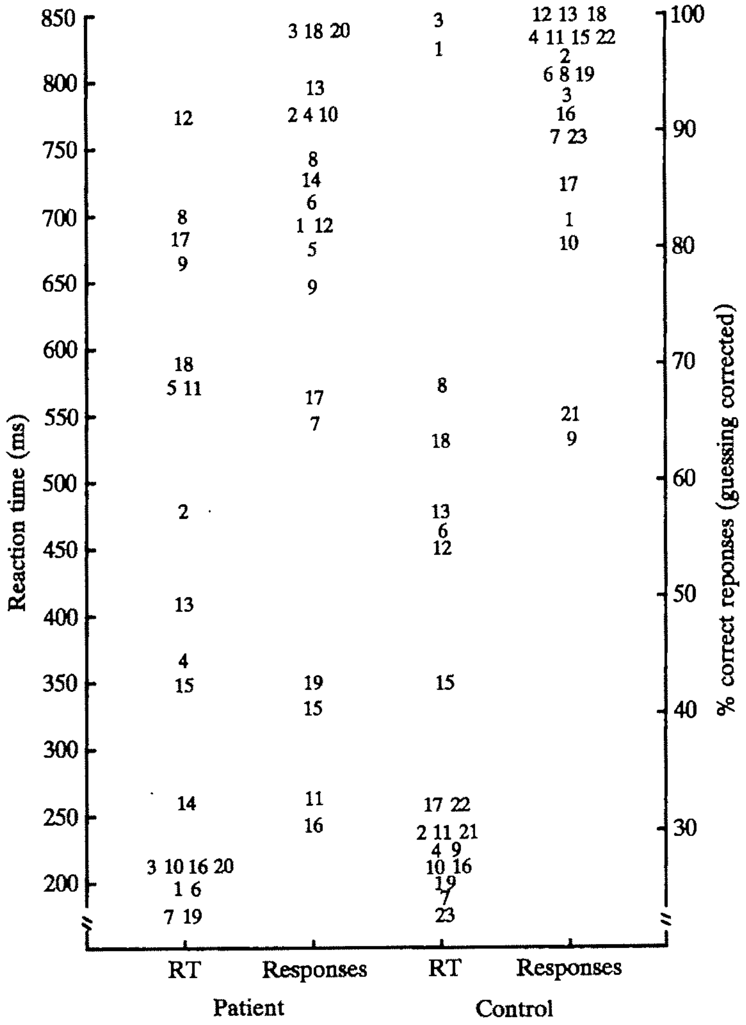

FIG. 4. RT and number of correct responses (corrected for guessing) for each member of the control and patient groups. Members of each group are identified by number, and patients belonging to each of three categories of PTA duration are indicated (*see* legend to fig. 3).

report (Curry, 1980, 1983). In contrast to controls, the patients' early CNVs did not differentiate GO and NO-GO trials, while their late CNVs showed smaller GO/NO-GO differences than the control group.

Overall, the lateral distributions of both the early and late CNV measures were very similar in the patient and control groups. However, the patients showed larger absolute interhemispheric asymmetries in the early CNV than did the controls. CNV asymmetries have previously been reported to accompany unilateral brain pathology (McCallum and Cummins, 1973), and it is possible that the enhanced asymmetries in the patients of the present study reflect a tendency for one hemisphere to receive more severe damage than the other. It is unclear why asymmetries in the early, but not the late CNV differentiated patients from controls in this manner, but this dissociation serves as a further example of the independence of these two regions of the CNV waveform.

No differences were observed between patients and controls in the amplitude or latency of the N1 component. It could be argued that the sampling rate employed in the present study (10 ms per point) was too slow to permit the detection of subtle differences between the groups. However, the null effects reported here are corroborated by the study of Rugg *et al.* (1988), which employed stimuli which were physically similar to those in the present study (80 dB, 250 Hz and 500 Hz tones), but which sampled the ERPs at the much faster rate of 3 ms per point. Rugg *et al.* found that neither the latency nor the amplitude of N1 differentiated head-injured patients from controls, although both variables differed as a consequence of whether the eliciting stimuli were targets or nontargets.

In the present experiment, the N1 component was reliably modulated by the GO/NO-GO manipulation, showing that some relatively early process discriminated between GO and NO-GO stimuli both in patients and controls. This suggests that the subsequent abnormally small GO/NO-GO differences in patients' waveforms do not simply reflect some relatively 'low-level' difficulty in distinguishing GO and NO-GO stimuli. Why the N1 should have distinguished GO and NO-GO stimuli is unclear, as this component is sensitive to a wide range of variables, ranging from the physical features of the eliciting stimuli to the level of 'arousal' of the subject (Näätänen and Picton, 1987). However, whatever the processes reflected by the GO/NO-GO differences in N1, they clearly were not sufficient to give rise to a GO/NO-GO difference in the patients' early CNV.

In contrast to the N1 component, frontal GO/NO-GO differences in the early CNV measure (300–600 ms post-S1) were a characteristic of the control group only. As noted in the Introduction, it has been argued that this region of the CNV, particularly from frontal electrodes, is associated with orienting processes. A number of studies have demonstrated sensitivity of the early CNV to such factors as the salience, or in Rohrbaugh's terminology, the 'signal value', of the eliciting stimuli (Rohrbaugh, 1984), and the present data from the control group would appear to be easily accommodated within such a framework. This would imply that for the patients, GO and NO-GO stimuli were equally salient, as the stimuli evoked frontal negative waves of equal amplitude. These waves were equal in magnitude to those elicited in the controls by GO stimuli, suggesting that the patients were over-responsive to the NO-GO stimuli, rather than under-responsive to the GO stimuli.

Following the early CNV, the waveforms for the controls showed an increasing separation between GO and NO-GO trials, and their NO-GO ERPs returned to baseline well before S2. The smaller and later separation of GO and NO-GO waveforms in the patients suggests less effective and less complete differential response preparation. This could be because the patients initially treated both S1 and S2 tones as signals indicating the need for response preparation, and only subsequently discriminated between GO and NO-GO trials. This could arise because head-injured patients are impaired in the speed with which they can categorize and respond differentially even to simple, easily discriminable, stimuli (van Zomeren *et al.*, 1984; Rugg *et al.*, 1988). Such a deficit may have led to slowness and uncertainty concerning the appropriate categorization of S1 stimuli, and to a strategy of initiating response preparation in response to either stimulus.

The foregoing account of the differing GO/NO-GO effects in patients and controls implies that the two groups differ 'quantitatively' rather than 'qualitatively', that is, the smaller and later GO/NO-GO differences in the patients reflect slowness in one or more components of an otherwise normal information-processing system, rather than a breakdown of that system. Evidence in favour of a qualitative difference between the patients and controls comes from the relationships observed between RT and the late CNV in the two groups. As might have been expected from previous work (Rohrbaugh and Gaillard, 1983), the controls showed a substantial positive correlation between the size of the terminal CNV and RT. This is compatible with the hypothesis that this region of the CNV reflects some aspect of pre-S2 motor preparation. No such correlation was found in the patients, raising the possibility that the normal linkage between prestimulus and poststimulus processing has become disrupted. This disruption might result from the adoption of different task strategies from those employed by the controls, compensating perhaps for impaired categorization speed, as discussed above. Alternatively, the CNV abnormalities might be reflecting more directly some aspects of brain damage common to the majority of head-injured patients.

Of the regions that may be of importance in this regard the frontal lobes are probably the most relevant here. The ERP measure that discriminated patients from controls most reliably (the early CNV) had a strong frontal distribution, and focal lesions of the frontal lobes are a common sequel of closed head injury (Stuss and Benson, 1986; Levin *et al.*, 1987). In addition, frontal regions have often been implicated in control processes responsible for the allocation of attention and the preparation and inhibition of responses, processes likely to be important in the GO/NO-GO task (Drewe, 1975; Verfaellie and Heilman, 1987). It is therefore of interest that out of the present sample of 20 head-injured patients, 9 had evidence of focal frontal damage (typically haematoma and/or contusion; *see* Table 1) on CT scans obtained shortly after injury. In addition, we were able to test 18 of the patients and 16 of the controls on the Wisconsin Card Sorting Test (WCST), which assesses the tendency to perseverate, and is sensitive to frontal lobe damage (Milner, 1963; Stuss and Benson, 1986). The patients made significantly more perseverative errors on this test ($P < 0.05$, Mann-Whitney test; *see* Tables 1, 2). This is consistent with the findings of Stuss *et al.* (1985), who also reported an excess of perseverative errors on the WCST as a long-term sequel to closed head injury.

Although radiological and neuropsychological evidence suggest that a significant proportion of the patients in the present sample might have damage to the frontal lobes, there was no association between these two indices (point biserial correlation between presence/absence of frontal CT abnormalities and WCST perseverative errors = 0.286). This is consistent with previous findings indicating that CT scans are poor predictors of neuropsychological test performance after head injury (Wilson *et al.*, 1988). Moreover, neither presence/absence of frontal CT abnormalities nor WCST performance correlated with early or late GO/NO-GO CNV difference scores. This may of course indicate that frontal pathology is not an important factor in accounting for the CNV abnormalities of head-injured patients. Alternatively, the lack of association between these measures may reflect the facts that (1) abnormal GO/NO-GO CNV waveforms and poor WCST performance may result from dysfunction of different frontal regions; (2) 'frontal' dysfunction following head injury may result not only from focal lesions, but also from the disruption of pathways to and from the frontal lobes, due to diffuse axonal injury (Stuss *et al.*, 1985); and (3) functionally significant lesions resulting from head injury are often not visible on CT scans (Jenkins *et al.*, 1986; Levin *et al.*, 1987). The employment of more sensitive indices of regional damage and dysfunction (e.g., MRI and PET) should allow a more conclusive assessment of whether the CNV abnormalities exhibited by head-injured patients do in fact correlate with dysfunction of frontal areas.

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SPATIAL CONTRAST SENSITIVITY IN UNILATERAL CEREBRAL ISCHAEMIC LESIONS INVOLVING THE POSTERIOR VISUAL PATHWAY

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SUMMARY

Contrast sensitivity function was studied in 16 patients with unilateral ischaemic lesions involving the posterior visual pathway. Sixty-two percent of the patients showed contrast sensitivity loss in at least one eye for horizontal or vertical stimulus orientation. Visual perception was distorted in a qualitatively different way according to the anteroposterior site of the lesion. Patients with occipital or occipitotemporal lesions showed high spatial frequency selective losses and patients with temporal or parietal lesions low frequency selective losses. Stimulus orientation selectivity was observed in patients with lesions of the primary visual cortex as well as in patients with lesions anterior to the striate cortex. Contrast sensitivity orientation-selective losses were demonstrated in 14 of the 17 'affected' eyes.

INTRODUCTION

The organization of the posterior visual pathway is known in general outline, but little is known about details of topography, and what perceptual deficits may occur under pathological circumstances. Acuity tests, as measured with Snellen letters, provide a good means for the detection of optic nerve and chiasmal disorders but have no value in the detection of unilateral lesions of the posterior visual pathway (Frisén, 1980). Acuity remains normal as long as either the crossing or the noncrossing neural outflow from the retinal fovea remains intact.

Nevertheless, in spite of clinically normal visual acuity, patients with cerebral lesions may complain of blurred vision (Bodis-Wollner and Diamond, 1976). Such patients might have a peculiar sort of visual disturbance, reducing central visual function, without affecting visual acuity. Such neurally-caused visual losses

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could be revealed by a more extensive test of central vision, determinations of spatial contrast sensitivity (CS).

Electrophysiological studies of single cells in the animal brain and psychophysical investigations of the human visual system have demonstrated that there may be parallel channels in the visual system, responding selectively to different spatial frequencies (Enroth-Cugell and Robson, 1966; Campbell and Robson, 1968; Blakemore and Campbell, 1969; Campbell *et al.*, 1969; Albrecht *et al.*, 1980). The overall bandwidth of frequencies narrows from the retina to the striate cortex where 'simple' cells have the narrowest bandwidth (Maffei *et al.*, 1973). This approach to vision assumes the existence of subsystems operating in parallel channels, each channel carrying a limited range of spatial frequencies. Functional disruption or anatomical lesions of the posterior visual pathway could selectively damage some frequency selective channels, while the others continue to function normally (Regan *et al.*, 1977, 1980, 1981). Such lesions can implicate central visual function without affecting visual acuity. CS examination as a function of spatial frequency might designate which part of the spatial frequency range is affected by different lesions compromizing the posterior visual pathway.

Another issue, concerning properties of neurons subserving central visual function, is orientation selectivity. Striate cortex neurons are not only sensitive to restricted ranges of spatial frequencies; they also appear sensitive to the orientation of the stimulus. Hubel *et al.* (1977, 1978) have demonstrated that orientation-selective neurons are organized in columns in the primary visual cortex. These orientation-sensitive neurons are not found peripheral to the primary visual cortex in primates. Orientation-selective CS loss, which has been described in multiple sclerosis (Regan *et al.*, 1980; Kupersmith *et al.*, 1984) and Parkinson's disease (Regan and Maxner, 1987; Bulens *et al.*, 1988) have therefore been explained in terms of involvement of cortical neurons. It is not surprising that true anatomical lesions of the posterior visual pathway can also generate abnormal CS function (Bodis-Wollner and Diamond, 1976; Kobayashi *et al.*, 1985). Measurements of spatial CS function for different orientations in this group of patients could yield information about visual perceptual deficits, not obtainable by conventional visual tests.

The purpose of this paper is to document CS function in patients with unilateral ischaemic lesions involving the posterior visual pathway. We were particularly interested in establishing whether CS function was affected in a qualitatively different way according to the site of the lesion, and whether orientation selectivity was restricted to lesions of the primary visual cortex.

SUBJECTS AND METHODS

Subjects

The control group consisted of 10 subjects without CNS disease. All were free of ocular disease. Subjects with known astigmatism were excluded. Snellen acuities, measured with refractive correction where necessary, were 10/10 or better. This group had a mean age of 68 yrs (range 56-84). Sixteen patients all having visual field defects consistent with unilateral cerebral ischaemic lesion and confirmed by CT scanning were selected. The duration after onset varied from 3 days to 10 yrs. All patients had an ophthalmological examination, including corrected visual acuity measurement and Goldmann perimetry. Patients with retinal abnormalities, lens opacity, or known astigmatism were excluded. The mean age of the patients was 65 yrs (range 53-77). The patients were classified according to the site of the lesion: occipital and occipitotemporal lesions (group I); temporal and parietal lesions (group II). Location and extent of lesions were determined from CT scans, referring to standard atlases (Gado *et al.*, 1979). Clinical summaries are given in Tables 1 and 2. Informed consent was obtained from all patients after the procedures had been fully explained.

Methods

Our methods have been described elsewhere in detail (Bulens *et al.*, 1988). Briefly, the stimuli consisted of gratings with a sinusoidal luminance profile generated on a video monitor (Bosch, type M 38 BA 487 TA). Contrast was measured to be linear up to 100% for all spatial frequencies used. The mean luminance for all stimuli presented was 5 cd/m². To avoid after-images, the phase of the gratings was alternated with a frequency of 0.8 Hz. The measuring technique used was based on a modified version of the Von Békésy tracking method, which is not 'criterion-free'. The subject reduced the contrast of the grating by depressing a push button. As soon as the contrast was subthreshold the button had to be released, which caused the contrast to increase. When the grating became just visible the subject depressed the button again. Repeating this process, the contrast of the grating varied around the subject's threshold. The higher and lower contrast-reversal values were averaged and this value was taken as the subject's threshold for that spatial frequency. To avoid adaptation effects the first four reversal values were not used. The mean value was determined by eight consecutive reversal points. The reciprocal value of these averaged results was plotted as a function of spatial frequency by a microprocessor on an X-Y plotter. It is known that in measurements using gratings consisting of less than 4-5 cycles, the CS is strongly dependent on the number of cycles presented (Campbell and Robson, 1968; Savoy and McCann, 1975; Van der Wildt *et al.*, 1976). To ensure that all gratings presented consisted of 4 or more cycles, it was not possible to measure CS for all spatial frequencies at one viewing distance. The monitor was therefore placed at a distance of 50 cm from the eye of the subject for spatial frequencies of 0.1-0.8 cycles/deg. For the higher spatial frequencies (0.8-25.6), the distance from the eye was automatically changed to 200 cm to compensate for limitations in the monitor system at high frequencies. For vertical gratings the rectangular screen subtended a visual angle of 32.5° horizontally and 23.5° vertically (spatial frequency 0.1-0.8 cycles/deg) and 8.5° and 6.0°, respectively, for spatial frequencies of 0.8-25.6 cycles/deg. For horizontal gratings the monitor was rotated. The visual angle of the stimulus field was 23.5° horizontally and 32.5° vertically (0.1-0.8 cycles/deg) and 6.0° and 8.5°, respectively, for spatial frequencies of 0.8-25.6 cycles/deg. The stimulus field was viewed in a dark surround. Each eye was tested separately.

RESULTS

Results from control subjects

The mean CS curves of the control group for vertical and horizontal stimuli are shown in fig. 1. Close inspection of individual CS curves in normal subjects can reveal that at intermediate spatial frequencies a CS curve can diverge slightly from the pure inverted U shape, based on theory and larger pools of performances. Such minor deflections of the CS curve at intermediate spatial frequencies were observed for vertical as well as horizontal stimuli. In 12 of the 20 measurements

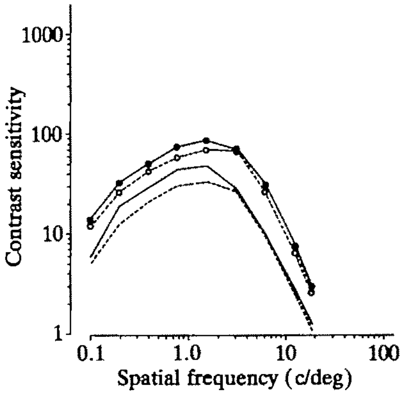

FIG. 1. Mean contrast sensitivity curve of 20 normal eyes for vertical (*filled circles*) and horizontal (*open circles*) gratings. Lines show 2 SD.

using vertical stimuli, slight decrements were found, while in 14 of the 20 measurements using horizontal stimuli such decrements were observed. The decrease factor (DF) of these decrements was defined as the ratio of the measured CS and the expected value of the nondiverged individual curve for a given spatial frequency (log/log). The mean DF of 26 measurements was 1.22±0.48 (2 SD). These slight decrements in the individual CS function of the controls are completely within intrasubject variability. There was no orientation-specific CS loss within the spatial frequency range.

Results from patients

The CS function for vertical and horizontal gratings of each of the patient's eyes was individually compared with the mean CS curves of the controls. A curve was judged abnormal when a CS deficit resulted in a displacement of a part of the curve below the control curve for more than 2 SD. Intermediate frequency loss was accepted as abnormal (notch defect) when the DF was more than 1.7 (log/log), being the mean DF in the normal group plus 2 SD. The width of the notch was defined as the spatial frequency bandwidth over which contrast loss was observed (octaves). Because in our test procedure mostly preselected spatial frequencies were used, we could only estimate an upper limit for the bandwidth. It is clear that the more intermediate CS values are measured the more accurate the width of a notch defect can be estimated. CS function was obtained in 32 eyes. Six patients had normal CS functions in both eyes for vertical and horizontal gratings. Of these 6 patients, 5 were in group I, and 1 in group II. Ten patients had at least one eye with CS deficit for either stimulus orientation; 3 of these 10 patients had a unilateral CS deficit for both stimulus orientations. The different types of CS loss for all patients are shown in Table 1. Contrast loss was confined to one eye for either stimulus orientation in 2 patients. CS loss was spatial frequency selective in all 'affected' eyes. Two patients (Cases 10, 16) showed a stimulus independent low frequency loss in one eye, all other CS deficits were

TABLE 1. CLINICAL DATA AND RESULTS OF NEURO-OPHTHALMOLOGICAL INVESTIGATIONS IN 16 PATIENTS WITH UNILATERAL ISCHAEMIC LESIONS OF THE POSTERIOR VISUAL PATHWAY

Case	*Sex*	*Age (yrs)*	*Duration after onset*	*Visual field*	*Visual acuity*	*Contrast sensitivity function*	
						Vertical stimuli	*Horizontal stimuli*
Group 1. Occipital and occipitotemporal lesions							
1	M	68	1 month	◐ ◐	R: 10/10	No loss	No loss
					L: 7/10	H loss	No loss
2	M	60	10 yrs	◑ ◑	R: 10/10	No loss	No loss
					L: 10/10	No loss	No loss
3	M	77	3 days	◑ ◑	R: 10/10	No loss	No loss
					L: 7/10	No loss	No loss
4	M	58	2 months	◑ ◑	R: 10/10	No loss	N loss(6.4–19.2)
					L: 10/10	N loss(9.4–19.2)	No loss
5	M	53	3 weeks	◑ ◑	R: 10/10	No loss	No loss
					L: 10/10	No loss	No loss
6	M	53	2 weeks	◑ ◑	R: 10/10	No loss	No loss
					L: 10/10	No loss	N loss(3.2–12.8)
7	F	61	9 months	◑ ◑	R: 15/10	No loss	No loss
					L: 15/10	No loss	No loss
8	F	75	1 month	◶ ◶	R: 10/10	No loss	No loss
					L: 8/10	No loss	No loss
9	F	72	18 months	◶ ◶	R: 10/10	N loss(6.4–19.2)	No loss
					L: 10/10	No loss	N loss(6.4–19.2)
Group 2. Temporal and parietal lesions							
10	M	72	2 months	◐ ◐	R: 8/10	N loss(0.2–0.8)	L loss
					L: 7/10	L loss	L loss
11	M	56	6 weeks	◑ ◑	R: 10/10	No loss	No loss
					L: 10/10	No loss	N loss(0.2–3.2)
12	M	67	1 month	◐ ◐	R: 10/10	N loss(0.2–0.8)	No loss
					L: 10/10	N loss(0.2–1.6)	N loss(0.8–3.2)
13	M	53	3 months	◴ ◴	R: 10/10	No loss	No loss
					L: 10/10	No loss	No loss
14	F	66	2 weeks	◴ ◴	R: 10/10	No loss	N loss(0.6–3.2)
					L: 8/10	N loss(0.4–1.6)	No loss
15	M	73	2 yrs	◐ ◐	R: 10/10	L loss	No loss
					L: 10/10	L loss	N loss(0.2–0.8)
16	F	76	4 yrs	◷ ◷	R: 7/10	L loss	L loss
					L: 7/10	No loss	No loss

R = right eye, L = left eye; L loss = low frequency CS loss, H loss = high spatial frequency CS loss, N loss = notch CS loss (spatial frequency range, cycles/deg).

orientation dependent. We measured intrasubject variability in 3 patients, by retesting CS two to three weeks later. The mean magnitude of variability was only 1.3±0.4 (2 SD), which means a high intrasubject test-retest consistency. The locations of the ischaemic lesions are summarized in Table 2, with particular emphasis on the visual cortical areas involved.

Group I: occipital and occipitotemporal lesions. Four of the 9 patients in this group had abnormal CS function in at least one eye for either stimulus orientation.

TABLE 2. LOCATION AND EXTENT OF ISCHAEMIC LESIONS IN 16 PATIENTS

Case	*Location* (*Brodmann areas*)
Group 1	
1	17, 18
2	17, 18, 19, 23, 31
3	17, 18
4	17, 18, 19, 20, 37
5	17, 18, 19
6	17, 18, 19
7	17, 18
8	18, 19
9	17
Group 2	
10	22, 28
11	21, 22, 37
12	20, 28, 34, 35, 37
13	20, 21, 38, 39, 40
14	Temporal genu of R optic radiation
15	39, 40
16	39, 40

All 6 'affected' eyes showed preferential loss at high spatial frequencies (above 3.2 c/deg); 5 of these 6 eyes showed a notch loss in the frequency range 3.2 to 19.2 c/deg. The mean bandwidth of these notches was 1.5 octaves (range 1–2). All CS deficits were stimulus orientation dependent. Involvement of Brodmann's cortical area 17 (striate cortex) was observed in 7 of the 9 patients (Table 2). All 4 patients with abnormal CS curves had involvement of area 17. Three patients with normal CS function, however, also had lesions of the striate cortex. Both patients with lesions of the peristriate areas (Cases 7, 8) and sparing of the primary visual cortex, had normal CS function for both orientations in the right and left eyes. Fig. 2 shows examples of orientation dependent CS loss in 2 patients. Case 4 illustrates orientation dependent CS loss in both eyes. A notch defect with a bandwidth of 1.5 octaves in the right eye for horizontal gratings and a notch defect of 1 octave in the left eye for vertical gratings. Both notches were centred at 12.8 c/deg. Case 6 shows a notch loss centred at 6.4 c/deg with a bandwidth of 2 octaves in the left eye for horizontal gratings only, and normal CS curves for both orientations in the right eye.

Group II: temporal and parietal lesions. Ten of the 14 eyes in this group showed CS loss at low spatial frequencies (below 3.2 c/deg), all but 2, orientation dependent. Notch defects (frequency range 0.2–3.2 c/deg) were seen in 7 eyes, all stimulus dependent. The mean bandwidth was 2.5 octaves (range, 2–4). All 7 patients in this group had no direct involvement of the striate cortex (Table 2). Eight of the 10 CS deficits, however, were nevertheless stimulus orientation-dependent. Detailed findings in 3 cases are shown in fig. 3. Case 10 shows a notch

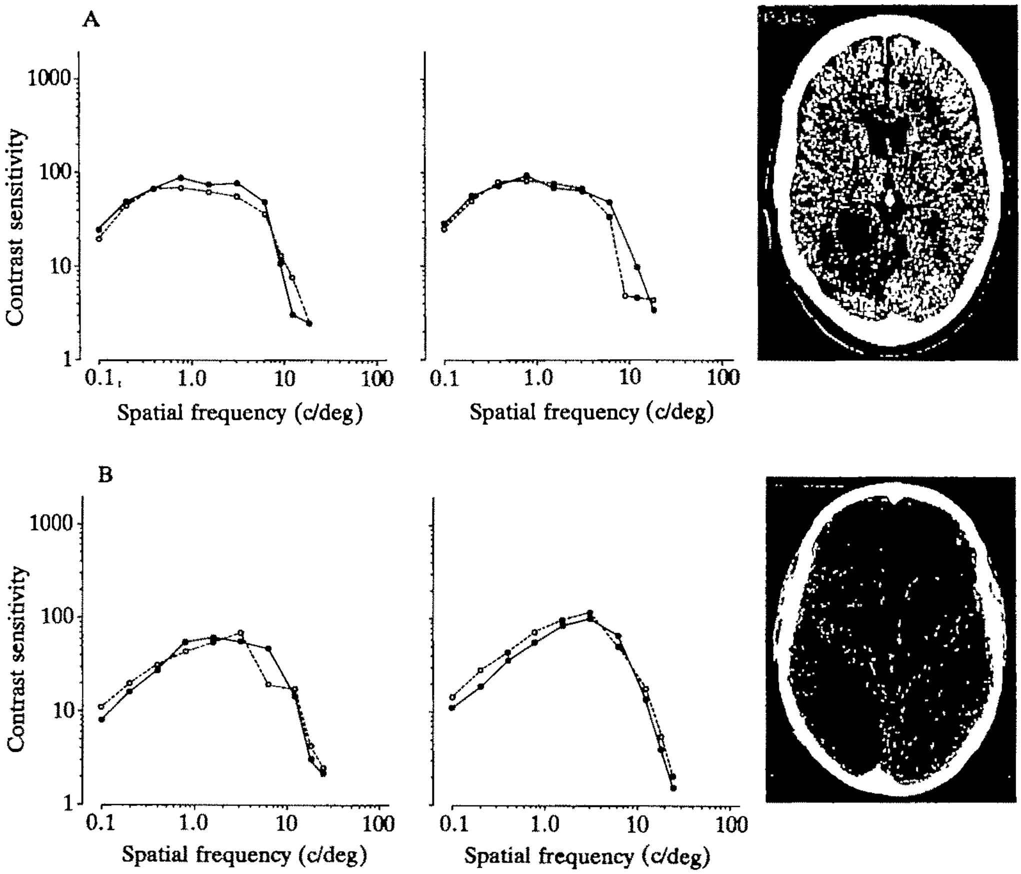

FIG. 2. CS curves and CT scans of A, a patient with a left-sided occipitotemporal infarct (*Case 4*) and B, a patient with a left-sided occipital lesion (*Case 6*). Key to symbols as in fig. 1. Orientation dependent CS loss in the high spatial frequency range, bilateral (Case 4) and unilateral (Case 6).

defect of 2 octaves centred at 0.4 c/deg for vertical stimuli and low frequency loss for horizontal stimuli in the right eye. Stimulus independent low frequency loss was seen in the left eye. Case 14 shows a notch defect 2 octaves in width, centred at 0.8 c/deg, in the left eye for vertical gratings and a 2.5 octaves wide notch defect centred at 1.2 c/deg in the right eye for horizontal gratings. Case 15 is an example of a patient with parietal infarction. Orientation dependent low frequency CS loss was demonstrated in both eyes for vertical gratings, and a notch defect with a bandwidth of 2 octaves centred at 0.4 c/deg was observed in the left eye for horizontal gratings. Clinical data of all patients are listed in Table 1.

DISCUSSION

Spatial CS function, elicited by sine wave gratings in 16 patients with unilateral ischaemic lesions involving the posterior visual pathway was abnormal in 62%.

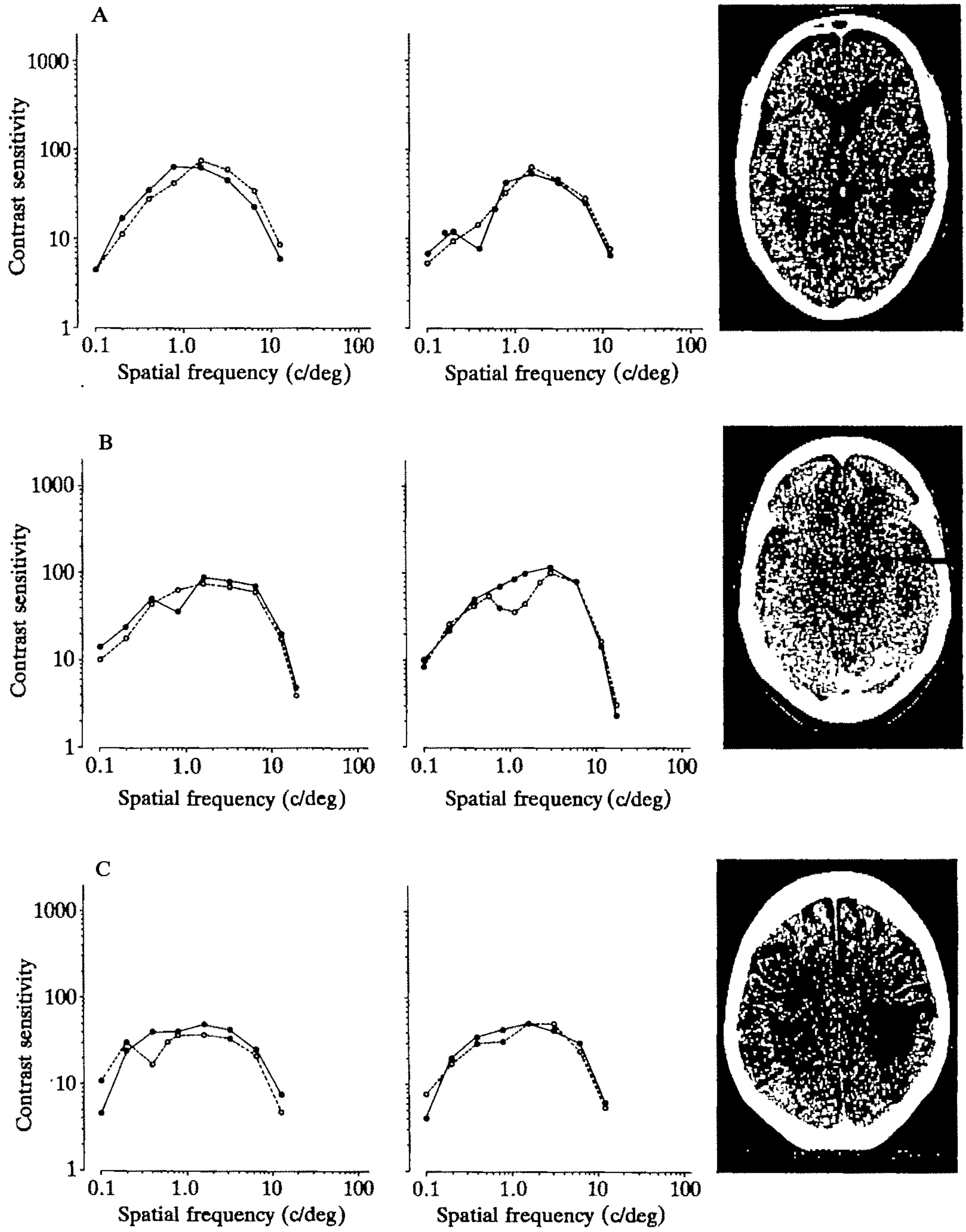

FIG. 3. CS curves and CT scans for A, *Case 10*, B, *Case 14* and C, *Case 15*. Arrow in B indicates right subinsular infarct affecting the genu of the right optic radiation. Case 10 (A) shows stimulus independent low frequency loss in the left eye, and stimulus dependent notch loss centred at 0.4 c/deg in the right eye. Both stimulus dependent notch losses in Case 14 (B) are also in the low spatial frequency range. Case 15 (C) shows orientation dependent low frequency loss in both eyes and a stimulus dependent notch loss at 0.4 c/deg in the left eye.

All patients had visual acuities of 7/10 or more. Visual perception was distorted in a qualitatively different way according to the site of the lesion. Visual losses restricted to medium and high spatial frequencies were confined to occipital and occipitotemporal lesions. Low spatial frequency losses were seen only in patients with temporal and parietal lesions. Monocular double vision was not encountered in our subjects, so that the observed notch defects could not have been produced by monocular diplopia. The mean width of the notch defects narrowed from 2.5 octaves in patients with temporal and parietal lesions to 1.5 octaves in patients with lesions affecting the visual cortex. Anatomical lesions of the posterior visual pathway can damage neurons with a restricted spatial frequency range, while others continue to function normally.

The CS measured for different orientations revealed that 14 of the 17 'affected' eyes showed orientation dependent visual loss. This stimulus orientation selectivity was observed in patients with lesions of the striate cortex as well as in patients with lesions anterior to the primary visual cortex. In 3 patients the CS loss was confined to one eye for either stimulus orientation. It is possible that CS measurements with more than vertical and horizontal stimuli may reveal more binocular CS deficits than those encountered in this study.

Our data confirm earlier reports of abnormal visuospatial CS due to cerebral lesions. Bodis-Wollner and Diamond (1976) found impairment of CS in 35 patients with cerebral lesions of heterogeneous aetiology. Four of these had unilateral posterior ischaemic lesions. Uniform loss was established in 2 patients, high frequency loss in 1 patient and notch losses at 6 and 14 c/deg were present in another patient. They concluded that cerebral lesions involving the human visual system have nonuniform effects on central vision. Kobayashi *et al.* (1985) studied CS function in 23 patients with cerebral infarcts involving the posterior visual pathway. They found abnormal CS function especially in patients with lesions of the nondominant parieto-occipital cortex. Their results are unfortunately based on the Arden grating test (Arden, 1978). This method generates substantial intrasubject variability. Moreover, their curves of CS function are almost flat, indicating a lack of difference in CS for low, intermediate and high spatial frequencies. Their data are in disagreement with the results obtained by all previous reports concerning CS measurements.

From psychophysical investigations of the human visual system and electrophysiological studies of single cells in the animal brain, many authors have proposed that visual input is processed via spatial frequency channels of unequal sensitivity (Enroth-Cugell and Robson, 1966; Campbell and Robson, 1968; Blakemore and Campbell, 1969; Campbell *et al.*, 1969; Albrecht *et al.*, 1980). According to this view, it has been suggested that the channels carrying low spatial frequencies have dissimilar characteristics from those dealing with high spatial frequencies (Lennie, 1980; Graham, 1981). The results of the present study seem relevant to the channel hypothesis. When we assume that the selective spatial CS losses in our patient groups indicate a dysfunction of one or more channels of a restricted range of spatial frequencies, lesions at different sites of the posterior visual pathway apparently affect different spatial frequency channels. In our study the affected spatial frequency range was systematically related to the anteroposterior site of the lesion. Contrast losses for spatial frequencies above 3.2 c/deg were only observed in patients with occipital and occipitotemporal lesions and losses for spatial frequencies less than 3.2 c/deg in patients with temporal and parietal lesions. Neural mechanisms in the anterior part of the postchiasmal visual pathway seem selectively sensitive (tuned) to low spatial frequencies, while high frequency tuning might exist in the posterior part, at the level of the primary visual cortex.

Visual neurons may be viewed as neural filters of visual signals, and spatial filtering properties can be measured by determining CS for a range of spatial frequencies. In animal studies spatial frequency selectivity for visual stimuli has been demonstrated in visual cortical neurons as well as in neurons of the retina and lateral geniculate body. Cortical neurons, however, are much more selective for spatial frequencies (highly tuned) than neurons of the retina or lateral geniculate body (Cooper and Robson, 1968; Campbell *et al.*, 1969; Maffei *et al.*, 1973; De Valois *et al.*, 1977, 1978, 1982). The degree of spatial tuning can be quantified in terms of the width of the spatial frequency selective CS loss (notch defect). These bandwidths are usually expressed in octaves. From electrophysiological studies of single cells in the animal brain it has been demonstrated that the band of spatial frequencies narrows from the retina to the primary visual cortex. The average bandwidth of visual cortical cells in cats is around 1.5 octaves (De Valois *et al.*, 1977, 1978; Tolhurst and Thompson, 1981) and by comparison, the average bandwidth in the lateral geniculate nucleus 4 to 5 octaves (So and Shapley, 1981; Thibos and Levick, 1983). The average bandwidth of the notch defect in our two patient groups also varied according to the anteroposterior site of the lesion. Although the distribution of bandwidths for a population of neurons is rather broad, and the ischaemic lesions of the patients in the present study are relatively large in some cases, the narrower average bandwidth of the notch defects in the patient group with (temporo)-occipital lesions (1.5 octaves) compared with the wider average bandwidth in patients with temporal and parietal lesions (2.5 octaves) is conspicuous.

Another issue, concerning properties of neurons subserving central visual function, is orientation selectivity. Orientation selectivity is a prominent attribute of primary visual cortex neurons (Hubel and Wiesel, 1962), so analysis has usually emphasized the distribution of orientation selectivity at that level (Hubel and Wiesel, 1962; Mansfield, 1974; Rose and Blakemore, 1974; Mansfield *et al.*, 1978). A particular point of interest in our results is that they indicate that orientation dependent loss is not restricted to lesions of the primary visual cortex. Orientation bias apparently also exists in the anterior parts of the postchiasmal pathway. Orientation selective CS loss is not confined to cerebral infarctions. Such losses have also been reported in multiple sclerosis (Regan *et al.*, 1980; Kupersmith *et* *al.*, 1984) and Parkinson's disease (Regan and Maxner, 1987; Bulens *et al.*, 1988) and have been explained in terms of involvement of cortical neurons.

Clinicopathological and radiographic studies have repeatedly accentuated the importance of the occipital striate cortex to human vision (Stensaas *et al.*, 1974). Electrophysiological studies in animals have demonstrated that the cortical visual areas are much more comprehensive than the striate cortex (Van Essen, 1979). In addition to striate cortex, at least 12 extrastriate areas have been demonstrated in the cat, and similar results have been found in primates (Van Essen, 1979; Tusa *et al.*, 1981). These studies have also shown the existence of nonoccipital areas that are involved in complex visual function. It has been demonstrated that there is an occipito-parieto-frontal pathway involved in spatial vision and an occipito-temporo-frontal pathway involved in object recognition (Denny-Brown and Chambers, 1976; Macko *et al.*, 1982; Mishkin *et al.*, 1983). Homologies between cortical areas of humans and other primates are not always clear, and the pattern of intercortical connections in the human brain is only partly understood. It is therefore difficult to compare the details of cerebral organization in different primates with that of man. Nevertheless, there is much evidence that the primary visual cortex in man has ample connections with surrounding association areas, the peristriate and inferotemporal cortex. Receptive field properties have been extensively analysed only for V1 in monkeys (corresponding to the striate cortex or Brodmann's area 17 in man). Neurons in secondary visual areas may also prove to respond selectively to spatial frequency and stimulus orientation. The functional columnar arrangement that clearly exists in V1 is not yet well demonstrated beyond V1. Experiments showing the effects of removing a visual area on receptive field properties of cells in areas prior to V1 are unknown. As monkeys in which V1 has been totally removed can still discriminate a wide variety of patterned stimuli (Butter *et al.*, 1980), the contribution to sensory analysis of pathways other than those from V1 is presumably far from unimportant.

Postchiasmal interference to the visual pathway produces a homonymous hemianopia, in spite of clinically normal visual acuity. When visual field defects encroach on the region of the field tested, orientation-selective CS loss may occur as a result of these field defects. In a simulation study, Hess and Plant (1986) demonstrated that various types of CS loss can be modelled by different types of visual field loss. A deficit maximal in the centre of the visual field affected high spatial frequencies, parafoveal deficit caused medium spatial frequency loss, and peripheral deficit gave rise to low frequency loss. Studies of CS across the visual field have shown that CS is maximum at the fovea for all spatial frequencies and falls off monotonically at increasing eccentricities (Robson and Graham, 1981; Regan and Beverley, 1983; Wright and Johnston, 1983; Plant and Hess, 1987). Visual field defects encountered in our patient groups are given in Table 1. Ten of the 16 patients had homonymous hemianopia, 9 of the 20 eyes showed normal CS function for both stimulus orientations, while the remaining 11 eyes showed various CS deficits ranging from low to high frequency CS loss. Multifocal types of CS loss were also observed in 6 patients showing homonymous quadrantanopia. Very different CS functions were thus found in patients showing similar visual field defects. It is therefore unlikely that uniform hemianopic involvement of the visual field encountered in our patient group could be related to the observed CS losses.

In conclusion, the results of our study attest to the hypothesis that visual processes are mediated by frequency selective channels. Orientation selectivity is not confined to primary visual cortex neurons, but also exists in the posterior visual pathway prior to the striate cortex.

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CYTOSKELETAL ABNORMALITIES IN MOTOR NEURON DISEASE

AN IMMUNOCYTOCHEMICAL STUDY

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SUMMARY

Immunocytochemistry with antibodies against cytoskeletal proteins has been used to search for molecular differences in the spinal cord from patients with motor neuron disease (MND) of amyotrophic lateral sclerosis type and normal spinal cord. Monoclonal antibodies which recognize phosphorylated neurofilament epitopes diffusely labelled a proportion of normal and MND anterior horn cells, but did not permit differentiation between normal and MND tissue. However, in some MND and control anterior horn cells, dense 'floccular' accumulations were labelled by antibodies recognizing phosphorylated neurofilament epitopes. These accumulations of phosphorylated neurofilaments suggest abnormalities of cytoskeletal regulation, but were neither a common nor a specific feature of MND. Axonal spheroids, which were as common in normal as in MND tissue, were labelled by all antineurofilament antibodies. Normal-appearing axons, but not spheroids, in MND and control tissue were identified by an antiactin antibody, indicating that actin may be absent from the cytoplasmic domain which gives rise to spheroids. In summary, we have not found specific posttranslational changes of cytoskeletal proteins in MND and, in particular, phosphorylated neurofilament epitopes are common to both MND and control anterior horn cells.

INTRODUCTION

Cytoskeletal abnormalities are prominent in the cellular pathology of neurodegenerative disorders, and understanding of molecular changes leading to accumulation of cytoskeletal proteins as neuronal inclusions may illuminate mechanisms of cell death in these conditions. In Alzheimer's disease (AD) the characteristic neurofibrillary tangles are composed of abnormal fibrous elements in the form of paired helical filaments (PHF); neurofilament (NF) and tau protein antigenic determinants have been identified as components of PHF (Anderton *et al.*, 1982; Gambetti *et al.*, 1983; Wood *et al.*, 1986). NF and tau proteins in tangles are phosphorylated to an extent that is unusual for these proteins in a perikaryal location (Grundke-Iqbal *et al.*, 1986). Normally, NF proteins in neuronal perikarya are nonphosphorylated or weakly phosphorylated, whereas axonal NF proteins

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are heavily phosphorylated (Sternberger and Sternberger, 1983; Shaw *et al.*, 1986). Thus the presence of phosphorylated cytoskeletal proteins in perikaryal inclusions in AD suggests that these proteins are inappropriately phosphorylated in this disease.

Abnormalities of the cytoskeleton are also a feature of motor neuron disease (MND) of amyotrophic lateral sclerosis type. They comprise axonal accumulations of ultrastructurally normal NFs (Wohlfart, 1959; Carpenter, 1968) termed spheroids and globules, and a variety of inclusions, mostly within anterior horn cells (Table 1). Since NF accumulations are particularly prominent in MND, the question arises as to whether NF proteins differ from those in normal tissue in their state of phosphorylation. Increased immunostaining by antibodies to phosphorylated NF epitopes has been observed in dorsal root ganglia (Moss and Lewkowicz, 1983; Rosenfeld *et al.*, 1987), spinal motor neurons (Moss and Lewkowicz, 1983; Goldstein *et al.*, 1987), and retinal ganglion cells (Dräger and Hofbauer, 1984) following nerve section or crush. In dorsal root ganglia this may be related to the site and type of neuronal damage and the extent of neuronal chromatolysis (Goldstein *et al.*, 1987). Massive accumulation of NFs in perikarya, dendrites, and proximal axons of motor neurons following experimental aluminium intoxication is associated with increased immunostaining of phosphorylated NFs, although in this case chromatolysis is not a feature (Troncoso *et al.*, 1986). These observations suggest that neuronal insults may result in maldistribution of phosphorylated NF epitopes. Definition of the distribution of phosphorylated and nonphosphorylated NF epitopes in MND may clarify the nature of the pathogenic process. We have used a number of well-characterized antibodies against cytoskeletal proteins to investigate possible molecular abnormalities in the composition of these proteins in anterior horn cells, normal appearing axons, and axonal swellings (spheroids) in spinal cord from a series of MND and control cases.

MATERIAL AND METHODS

Spinal cord tissue

Autopsy material was available from 10 patients with MND, aged 40–74 yrs (mean 60 yrs) at death. In each case the diagnosis had been established after full neurological investigation, and characteristic changes were found in the central nervous system. There were 4 women and 6 men. Tissue from 4 of these cases was used in a previous study (Swash *et al.*, 1986). We also examined 13 control cases, consisting of 7 women and 6 men aged 34–83 yrs (mean 63 yrs) at death; 7 had died of acute myocardial infarction, and the others of various acute and chronic illnesses. Only 3 were known to have had neurological abnormalities; 1 suffered anoxic brain damage following resuscitation after a cardiac arrest, 1 died 24 h after an acute intracerebral haemorrhage, and 1 died as a result of carcinomatous meningitis. In the controls, postmortem examination was made 11–120 h (mean 40 h) after death; these data were not known in the MND cases.

Spinal cords from 4 of the MND and all the control cases were fixed suspended in 10% buffered formalin for 2 wks before embedding, but material from 6 of the MND cases had been stored in formalin for several years. Blocks from L4 (or in 3 MND cases, C8) segment were processed for immunocytochemistry as previously described (Anderton *et al.*, 1982).

TABLE 1. CELLULAR INCLUSIONS IN MOTOR NEURON DISEASE

Inclusion	*Site*	*LM appearance*	*EM appearance*	*Component proteins*	*Specificity/frequency*
1. Spheroids	Axons and ACHs in spinal grey matter	Rounded swellings, 10–100 μm diameter, hyaline, eosinophilic, argyrophilic	Masses of 10 nm filaments	NFs, P +ve and P −ve epitopes	Nonspecific; seen in most controls and MND cases
2. Hyaline bodies	AHCs in spinal grey matter	Homogeneous, eosinophilic aryrophilic conglomerates	Masses of 10 nm filaments	NFs, P +ve and P −ve epitopes	Not seen in controls; present in some sporadic and familial cases
3. Bunina bodies	AHCs in spinal grey matter	Eosinophilic, rounded or elongated, single or multiple masses, 1–4 μm diameter	Complex, variable; vesicles with filamentous tubules, 70–80 nm diameter; small vesicles, electron dense granules	Not known	Specific for MND; seen in about 70% of cases
4. Basophilic bodies	AHCs in spinal grey matter	Basophilic, 'globoid' or 'asteroid' shapes, 3–4 μm diameter	Complex, irregular chains containing filamentous or 'fuzzy' structures, with rough ER, glycogen, small vesicles and mitochondria; ?related to Bunina bodies	Not known	Majority of cases; not seen in controls
5. Tubular particles	Axons and AHCs in spinal grey matter	Not detected	Round, membrane-bound or free in cytoplasm; 10–15 nm or 28 nm diameter. May appear solid or tubular	Not known	Reported in 6 ALS cases; not seen in controls
6. Pericapillary bodies	Capillary wall and BM in spinal cord	Eosinophilic, single or multiple, 0.5–8 μm ovoid bodies	Paracrystalline structures with tubular structures 25–40 nm diameter	GFAP-positive	Occasionally seen in controls
7. Hirano bodies	Perikarya and dendrites of AHCs; axons in spinal grey matter	Eosinophilic rod-shaped bodies, 4–6 μm diameter	Lattice-like or parallel arrays of fine 6–10 nm filaments	Actin; α-actinin; tau; tropomyosin; vinculin	Nonspecific
8. Granulovacuolar degeneration	AHCs	Clear vacuoles, 3–5 μm diameter containing 1 μm granules	Membrane-bound inclusions with dense granular core	NFs; P +ve epitopes	Seen in Guam ALS-PD-dementia
9. Lewy bodies	AHCs; occasionally extracellular in spinal grey matter	Eosinophilic concentric bodies with dense core and lightly staining halo, 7–20 μm diameter	Dense core of granular material; outer zone of radially arranged filaments, 10 nm diameter	NFs, mainly in halo; P +ve and P −ve epitopes	About 15% of cases

AHCs = anterior horn cells; ALS = amyotrophic lateral sclerosis; BM = basement membrane; NFs = neurofilaments; P +ve = phosphorylated, P −ve = nonphosphorylated epitopes.

References

1. Carpenter, 1968; Chou, 1979; Hirano, 1982; Clark *et al.*, 1984; Delisle and Carpenter, 1984; Schmidt *et al.*, 1987.
2. Hirano *et al.*, 1967; Kondo *et al.*, 1986.
3. Bunina, 1962; Chou, 1979; Hirano, 1982.
4. Chou, 1979.
5. Norris *et al.*, 1975; Chou, 1979; Averback, 1981.
6. Averback, 1986.
7. Chou, 1979; Goldman, 1983; Galloway *et al.*, 1987*a*, *b*.
8. Hirano *et al.*, 1968; Kahn *et al.*, 1985; Goldman and Yen, 1986.
9. Chou, 1979; Goldman *et al.*, 1983; Schmidt *et al.*, 1987.

Antibodies

We used four monoclonal antibodies (MAbs) against NF proteins (RT 97, BF 10, 147, and RS 18), one MAb against G-actin (D 27) and polyclonal antibodies (PAbs) against purified tau protein, PHF, and dephosphorylated NF heavy chain (Table 2).

TABLE 2. CHARACTERISTICS OF ANTIBODIES USED FOR IMMUNOCYTOCHEMICAL STUDIES*

Monoclonal antibody	*Antigen specificity*	*Epitope location*	*Labelling of AD tangles in situ*
RT 97	NF-H, NF-M	NF side arm	All or most
147	NF-H, NF-M	NF side arm	None
BF 10	NF-M	NF side arm	All or most
D 27	G-Actin	—	—
Polyclonal antibody			
Anti-NF-H	Purified, dephosphorylated NF-H polypeptide; also labels NF-M	—	None
Anti-PHF	Partially purified PHF	—	All or most
Anti-tau	Purified tau protein	—	All or most

* References given in text. AD = Alzheimer's disease; NF-H = neurofilament heavy chain polypeptide; NF-M = neurofilament medium chain polypeptide; PHF = paired helical filaments.

Characteristics of some of these antibodies have been described elsewhere (Miller *et al.*, 1986; Haugh *et al.*, 1986; Brion *et al.*, 1987; Duyckaerts *et al.*, 1987). RT 97, BF 10, 147, and RS 18 label predominantly phosphorylated NF epitopes, and RT 97 and BF 10 label AD tangles, whereas 147 and RS 18 do not. The epitope detected by these MAbs is located on the NF side arm. Anti-NF-H (J. Kahn *et al.*, unpublished results) is a polyclonal antibody against purified bovine neurofilament proteins treated with alkaline phosphatase. This antiserum reacts with phosphorylated and dephosphorylated forms of NF-H, and to a lesser extent with NF-M. MAb D 27 was prepared by fusing spleen cells from balb/c mice immunized with 3T3 cell Triton-X-100 insoluble proteins and was found to label purified G-actin (J. Kahn *et al.*, unpublished results). For immunocytochemistry, serial sections were processed with ascites fluid (MAbs) or antisera (PAbs) at three dilutions which had been identified as giving the most satisfactory specific staining in pilot experiments. For each antibody, control sections were also processed in the absence of primary antibody.

Analysis of sections

Neurons, spheroids, and normal-appearing axons were identified on sections stained with haematoxylin and eosin, and on immunocytochemically stained serial sections. In addition, the latter were counterstained with haematoxylin. Bunina bodies were identified in haematoxylin and eosin stained sections. Counts were made of all anterior horn cells and spheroids in one representative section labelled with MAbs RT 97, BF 10, 147, RS 18 and PAb NF-H, as well as in one haematoxylin and eosin stained section, for each MND and control case. For the quantitative analysis of antibody labelling, one section (from a series of three at different antibody dilutions) which showed specific labelling (i.e., intense staining of axons and/or neurons with minimal background staining) was chosen, and anterior horn cells classified as positive or negative for antibody labelling. In addition, we noted whether anterior horn cell labelling was diffuse or focal, and whether there were 'floccular accumulations', by which we mean deposits of anti-NF positive material in irregular, condensed accumulations within the perikarya. Quantitative data were analysed using Student's t test.

RESULTS

Loss of anterior horn cells in MND cases was variable, but there were significantly fewer anterior horn cells in MND spinal cord compared with controls. The mean number of anterior horn cells per section in haematoxylin and eosin stained sections was 42±15 (SD) for the 10 MND cases compared with 85±18 (SD) in the 13 controls ($P < 0.001$), and similar counts and significance levels were obtained from immunolabelled sections (Table 3). In some MND cases very few anterior horn cells remained, and there was marked gliosis in the ventrolateral grey matter. Some hyaline neurons showing achromasia were seen in most MND cases. Bunina bodies (Bunina, 1962) were seen in 3 MND cases, but we did not observe Lewy-like bodies or Hirano bodies in our material. We were not able to identify Bunina bodies with the antibodies used in this study. In control spinal cord, occasional hyaline neurons were seen, and in 1 case such neurons were plentiful in the ventromedial anterior horn of L4 bilaterally. This was a 44-yr-old man with no known past history of neurological disease admitted following a myocardial infarct, who had a cardiac arrest, was resuscitated and survived for 48 h, during which time he had generalized seizures and evidence of diffuse brain damage. The cause of the achromasia and hyaline change in this case remains uncertain, but is likely to be related to anoxia.

The quantitative analysis of immunolabelled sections is summarized in Table 3.

TABLE 3. QUANTITATIVE STUDIES OF ANTINEUROFILAMENT ANTIBODY LABELLING IN MND AND CONTROL SPINAL CORD

A. Total counted neurons per section (mean±SD), and percentage (±SD) of anterior horn cells positively labelled by MAbs 147, BF 10, and RS 18, and by anti-NF-H

Antibody	*MND (n = 10)*		*Control (n = 13)*	
	Total no.	*% positive*	*Total no.*	*% positive*
Anti-NF-H	42±18**	95±9.5	82±18	91±10
147	32±15**	18±27	70±18	45±35
BF 10	42±17**	11±17	67±15	41±28*
RS 18	34±14**	12±11	64±15	39±34*

* $P = < 0.01$, comparing percentage of positive neurons in MND and control tissue; ** $P = < 0.001$ comparing total numbers of neurons per section in MND and control tissue (unpaired Student's t test).

B. Numbers of axonal swellings per section in anterior horns from MND and control spinal cord

Antibody	*MND (n = 10)*	*Control (n = 13)*
Anti-NF-H	16±24	32±18 n.s.
147	48±77	44±27 n.s.
BF 10	44±65	53±33 n.s.
RS 18	32±24	45±32 n.s.

n.s.: $P = > 0.05$ (Student's t test).

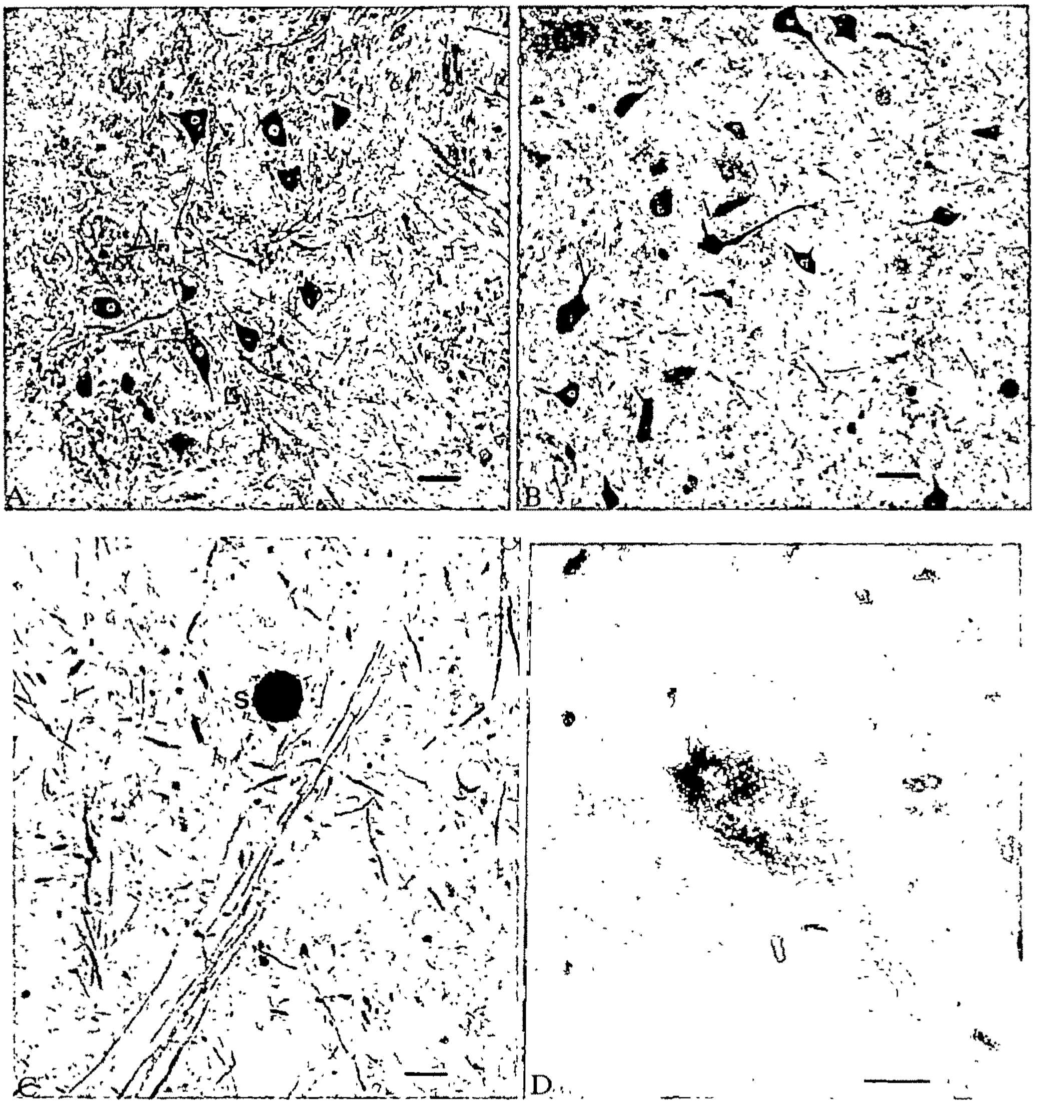

FIG. 1. A, MND, anti-NF-H: ventral anterior horn at L4 segment. Neurons appear shrunken and are reduced in number but all surviving neurons are labelled. Bar = 50 μm. B, normal control, anti-NF-H: ventral anterior horn at same level. Bar = 50 μm. C, MND, MAb 147: L4 anterior horn grey matter showing intensely labelled spheroid (S), and anterior horn cells which are unlabelled. Bar = 20 μm. D, MND, MAb 147: L4 anterior horn cell showing diffuse, relatively homogenous neurofilament labelling in one part of the perikaryon, apparently related to an accumulation of lipofuscin in another portion of the cell. Bar = 10 μm.

Anti-N-H labelled over 90% of MND anterior horn cell perikarya and dendrites in control and MND cases (fig. 1A, B). RT 97 labelled very few anterior horn cells in MND and control tissue, possibly because labelling by this MAb is particularly sensitive to duration of fixation (Connolly *et al.*, 1987). A significantly lower proportion of anterior horn cells were labelled by MAbs BF 10 and RS 18 in

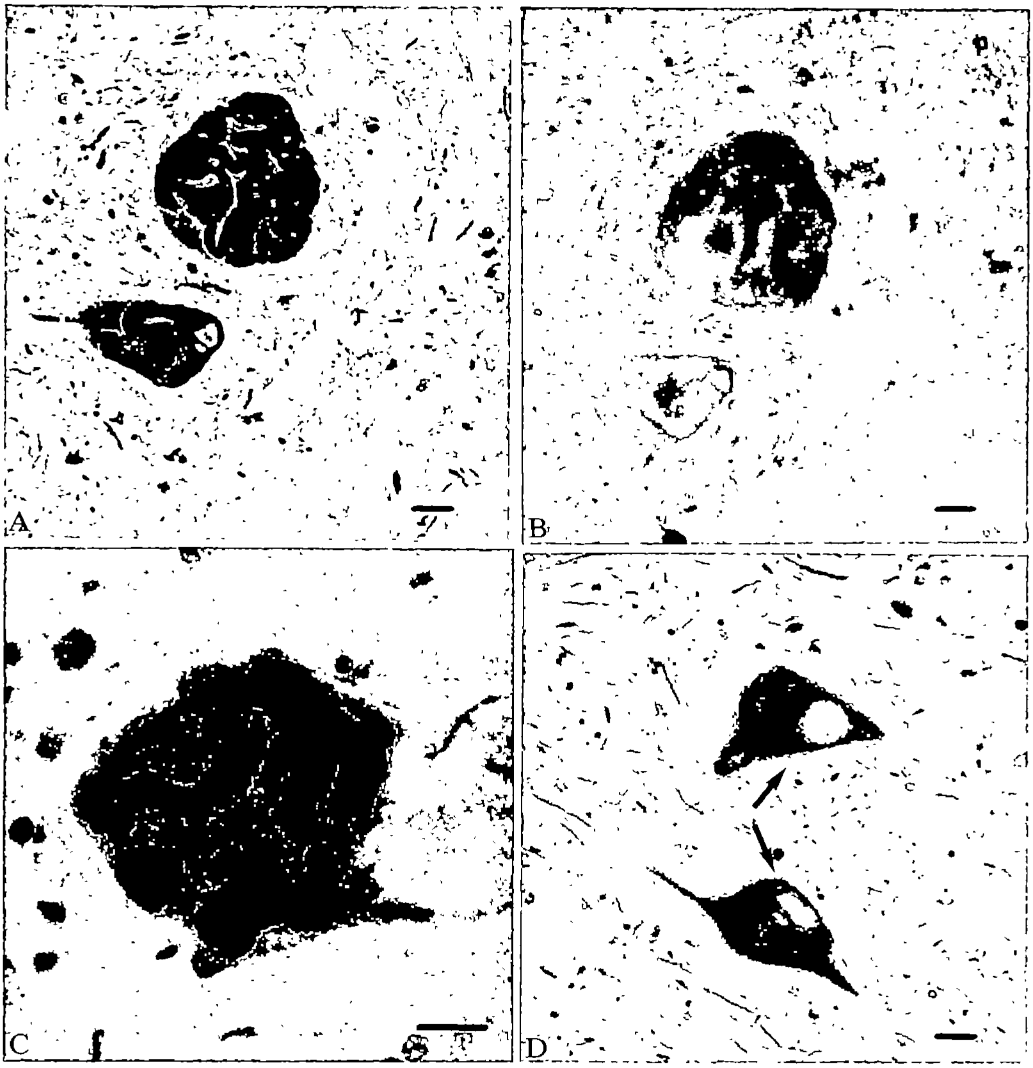

FIG. 2. A, MND, anti-NF-H: 'floccular' inclusions in abnormal anterior horn cells. Bar = 20 μm. B, the same neurons, MAb BF 10: although labelling is less intense than with anti-NF-H, the convoluted floccular inclusions are labelled with this MAb. Bar = 20 μm. C, abnormal anterior horn cell from control case with carcinomatous meningitis, labelled with MAb RT 97. The convoluted floccular inclusions are identical to those illustrated in A and B. Bar = 20 μm. D, abnormal anterior horn cells from L4 segment of patient who sustained severe anoxic brain damage following cardiac arrest: MAb RT 97. Whereas normal appearing neurons were unlabelled by anti-NF MAbs, neurons showing achromasia (arrowed) were intensely labelled by MAbs directed against phosphorylated NF epitopes. Bar = 20 μm.

MND compared with control spinal cord; a similar trend was seen with 147, but the difference was not statistically significant. Neurons which were labelled by these MAbs were usually lightly and diffusely labelled (fig. 1C, D) but some hyaline-appearing anterior horn cells in 1 MND and 1 control case contained dense 'floccular' accumulations of NF-positive material which were strongly labelled by all NF MAbs and by anti-NF-H (fig. 2A, C). This control case was a man who died with carcinomatous meningitis; his spinal cord showed meningeal infiltration with poorly differentiated adenocarcinoma cells, but most anterior horn cells were normal in appearance and there was no loss of anterior horn cells. Intense but diffuse labelling of hyaline anterior horn cells was also seen in the control case who died following a period of anoxia (fig. 2D). Normal-appearing anterior horn cells in MND and control material sometimes contained focal accumulations of NF positive material, but these were weakly labelled and finely granular rather than intensely staining and floccular (fig. 1D). This appearance was often associated with accumulations of lipofuscin.

Axonal swellings (globules and spheroids) were seen in the ventral grey matter in all control cases and in all but 2 of the MND cases (figs 1C, 3A). Absence of axonal swellings in MND tissue was associated with severe loss of anterior horn cells and marked gliosis of grey matter. Normal-appearing axons, as well as axonal swellings in both MND and control material were labelled by all anti-NF MAbs, although RT 97 produced the weakest labelling. There were no statistically significant differences in the numbers of axonal swellings between MND and control cases with any of the anti-NF antibodies tested (Table 3), although on average there were proportionally more axonal swellings per anterior horn cell in the MND cases than in controls.

MAbs 147, BF 10, and RS 18 each labelled similar numbers of axonal swellings. Anti-NF-H identified fewer axonal swellings than these MAbs, but this difference was not statistically significant. D27, an anti-actin MAb, labelled normal appearing axons in control and MND tissue but never labelled axonal swellings (fig. 3B). Apart from very light diffuse labelling, neither MND nor control anterior horn cells were labelled by this antibody. Anti-PHF yielded diffuse staining of neurons, axons and spheroids but with almost equally intense background staining in normal and pathological tissue. The anti-tau antiserum failed to label any structures under these conditions.

DISCUSSION

Changes in the molecular structure of cytoskeletal proteins may affect neuronal integrity and survival. Microtubules, with NFs, form the ultrastructural components of the cytoskeleton, and are responsible for axonal transport (Robinson and Anderton, 1988). Other putative functions of the cytoskeleton include regulation of the size and shape of neurons and determination of axonal calibre (Hoffman and Lasek, 1980; Hoffman *et al.*, 1984). Abnormalities of NF and microtubule proteins have been identified in the characteristic inclusions of Alzheimer's, Parkinson's and Pick's diseases (Anderton *et al.*, 1982; Gambetti *et al.*, 1983; Kahn *et al.*, 1985; Grundke-Iqbal *et al.*, 1986; Haugh *et al.*, 1986; Miller *et al.*, 1986; Price *et al.*, 1986; Wood *et al.*, 1986). A wide variety of neuronal inclusions have been described in MND, the most striking being accumulations

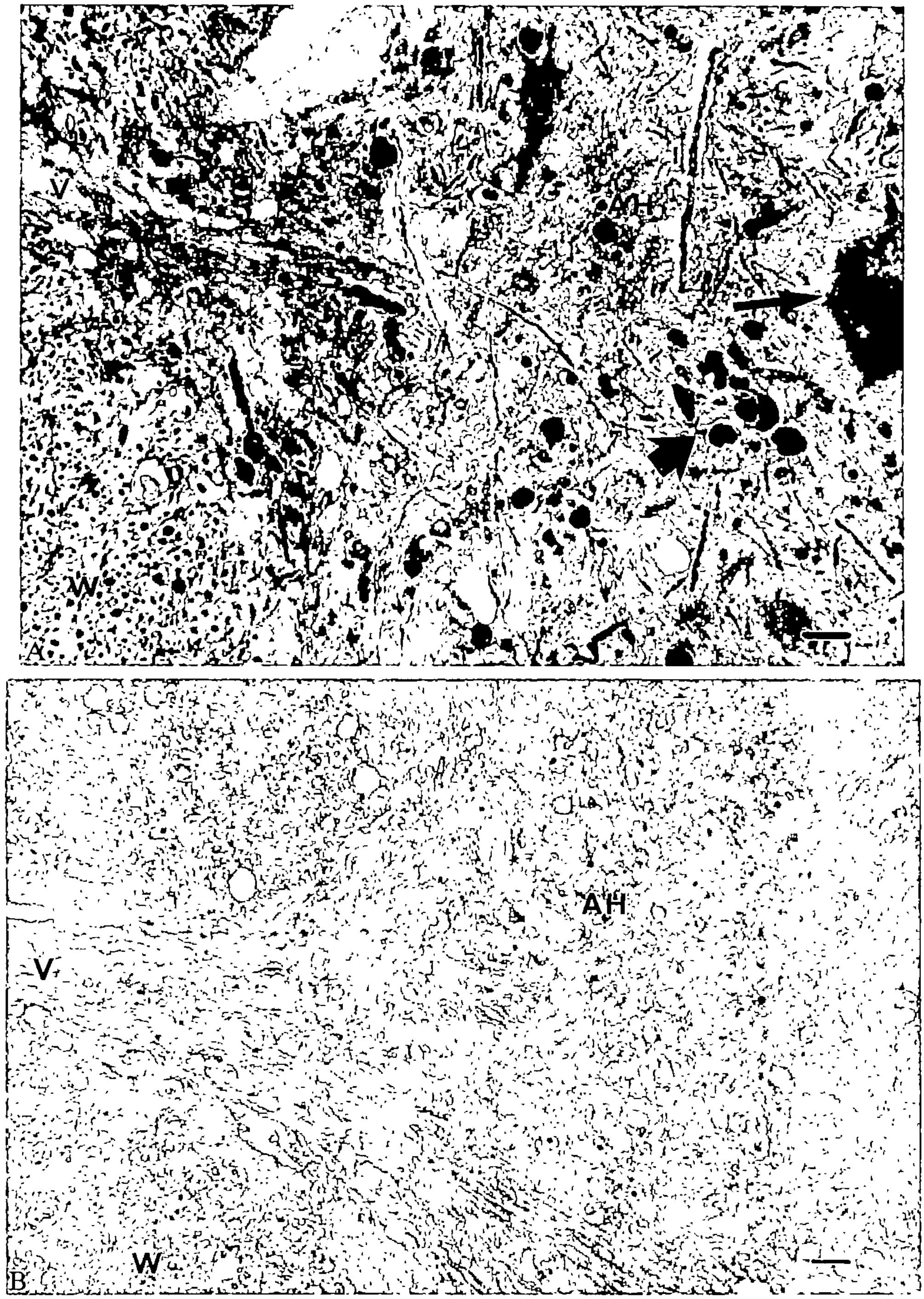

FIG. 3. A, *control case*, MAb 147. Ventral anterior horn showing ventral root exit zone (V), ventral white matter (W), axonal swellings (large arrow) and diffusely labelled anterior horn cell (small arrow). Bar = 20 μm. B, same case, MAb D 27, showing same region. Axons and neuropil are labelled, but no axonal swellings are discernible. Bar = 20 μm.

of normal appearing neurofilaments within axons and less commonly anterior horn cells (Table 1).

We have been unable to show differences in the molecular structure of NF proteins in normal and MND spinal grey matter, as related to the epitopes recognized by our antibodies. This does not mean, however, that structural or molecular differences do not exist, since antibody binding to an individual epitope relates only to the structure of a small proportion of the polypeptide. Our observations are in accord with those of Schmidt *et al.* (1987) who used a battery of MAbs which differentially identified phosphorylated or nonphosphorylated NF epitopes. They studied only 2 MND cases, but neurons from these revealed similar NF determinants to those from controls.

In our studies, normal and MND anterior horn cells were labelled by anti-NF MAbs directed against phosphorylated NF epitopes, but no specific pattern to this labelling was observed. Indeed, positive labelling of anterior horn cells was more frequent in normal than in MND spinal grey matter. Our findings do not suggest that in comparison with control tissue MND anterior horn cells contain abnormally phosphorylated NF epitopes. When labelling of MND or control anterior horn cell perikarya occurred, it was usually diffuse, and the majority of such neurons appeared normal. Anti-NF-H labelled the majority of anterior horn cells, in keeping with its predilection for nonphosphorylated NFs which are distributed mainly in neuronal perikarya, dendrites, and proximal axons (Sternberger and Sternberger, 1983), suggesting that this normal pattern of distribution of phosphorylated and nonphosphorylated NF proteins is maintained in most MND anterior horn cells.

Our observations on the pattern of diffuse labelling of anterior horn cells differ somewhat from those of Munoz *et al.* (1988) who used a MAb (NF2F11) which recognizes phosphorylated NF epitopes. In contrast to our findings, they concluded that more MND than control anterior horn cells were diffusely labelled, although the difference was not statistically significant. However, when NF2F11-positive cells were divided into three categories according to the nature of the neuronal abnormality, they concluded that diffuse staining of abnormal-appearing neurons, and staining of focal neuronal NF accumulations, was more common in MND than in controls. They noted 'focal accumulations' of NF2NF11-positive material in anterior horn cells in 7 of their 9 MND cases and suggested that these accumulations, which hitherto have been noted particularly in familial cases (Hirano *et al.*, 1967) are also a common feature of sporadic MND. In view of the difficulties of accurately classifying neurons as normal or abnormal, we did not attempt to make a quantitative analysis in this way. Furthermore, in only 1 MND case did we see anterior horn cells containing massive focal inclusions which were intensely labelled by anti-NF antibodies. These occurred in grossly abnormal neurons, which in adjacent haematoxylin and eosin sections appeared hyaline and showed achromasia. We also observed such neurons in the spinal cord of a man who died with carcinomatous meningitis, so this appearance is not specific for

MND. We distinguished between massive focal ('floccular') accumulations and the common 'localized' immunolabelling of anterior horn cell cytoplasm. The latter was apparently related to accumulations of lipofuscin displacing NF-immunoreactive cytoplasm from one pole of the neuron. It appears that Munoz *et al.* (1988) would classify this appearance as 'focal accumulation' of NFs.

We agree, however, with Munoz *et al.* (1988) that abnormal hyaline anterior horn cells which contain dense accumulations intensely labelled by MAbs against phosphorylated NF epitopes are not seen in normal spinal cord. Such changes may reflect an axon reaction (Moss and Leukowicz, 1983; Goldstein *et al.*, 1987; Rosenfeld *et al.*, 1987) but do not permit definite conclusions as to the site of neuronal damage, particularly as damage to anterior horn cell processes is not inevitably associated with central chromatolysis or the appearance of phosphorylated NF epitopes within the perikaryon (Goldstein *et al.*, 1987).

We found no evidence that axonal swellings in MND spinal cord were either more abundant, or different in the distribution of NF epitopes tested, compared with control tissue. Our findings are in keeping with the notion that in MND and normal spinal cord apparently normal NFs accumulate in proximal axons possibly as a result of altered axonal transport of NF and other cytoskeletal proteins (Chou, 1979; Griffin *et al.*, 1982; Hirano, 1982; Schmidt *et al.*, 1987). Although we cannot be certain, the results suggest that MAbs 147, BF 10 and RS 18 identify the same population of axonal swellings. Counts of anti-NF-H labelled axonal swellings revealed a trend towards lower counts than obtained with the anti-NF MAbs, although this was not statistically significant. If this trend reflects a real phenomenon, it would be compatible with the idea that NFs are increasingly phosphorylated as they progress from perikarya to the peripheral axons (Sternberger and Sternberger, 1983; Robinson and Anderton, 1988).

The present findings do not clarify the mechanisms which may result in NF accumulation or abnormal axonal transport, but our observation that a MAb against actin labels normal appearing axons but not axonal swellings implies that actin may be excluded from the cytoskeletal domain related to axonal swellings. The significance of this is uncertain. Actin is a contractile protein which exists in neurons mainly as monomeric subunits and short filaments, and is implicated in maintaining dendritic shape and axonal transport (Caceres *et al.*, 1983; Goldman and Yen, 1986; Kobayashi *et al.*, 1986). In normal axons actin is localized mainly beneath the axonal membrane where it is associated with microtubules (Papasozomenos and Payne, 1986; Tsukita *et al.*, 1986). However, in β,β'-iminodipropionitrile (IDPN) treated axons, actin and microtubules are redistributed to the central region of the axon and excluded from the subaxolemmal region. Axonal swellings are a prominent feature of IDPN toxicity. Since the central region has been associated with fast axonal transport (Kobayashi *et al.*, 1986) actin may be implicated in this aspect of axonal function. Of interest therefore is the recent observation that fast retrograde transport is impaired in MND motor nerve fibres (Breuer *et al.*, 1987). It remains to be seen whether abnormalities of actin or microtubule structure or distribution contribute to axonal and neuronal damage in MND.

In summary, NF protein determinants detected by our antibodies are similar in anterior horn cells of MND and control spinal cord. In MND, hyaline anterior horn cells which show achromasia may show dense accumulations of abnormally phosphorylated NFs, but such changes may not be specific for MND. The relationship between these changes and the axon reaction is unknown. Experimental approaches which clarify the pathogenesis of neurofilamentous inclusions in anterior horn cells and axons may clarify the site and type of neuronal injury in MND.

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ELECTROPHYSIOLOGICAL INVESTIGATIONS IN ADOPTIVELY TRANSFERRED EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS IN THE LEWIS RAT

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SUMMARY

Lewis rats with experimental autoimmune encephalomyelitis transferred adoptively with myelin basic protein-specific T line cells (AT-EAE) were studied clinically, electrophysiologically, and histologically. Injection with 5×10^6 line cells induced EAE with a rapidly developing tetraplegia after a latent period of 4 days. Electrophysiological testing revealed a profound slowing of afferent conduction within the dorsal column of the spinal cord, and conduction abnormalities in the spinal roots. Injection with a lower cell dose of 1×10^6 T line cells caused only moderate clinical signs paralleled by milder conduction slowing and conduction failure. Light microscopy showed marked inflammation with infiltration of mononuclear cells and some demyelination throughout the spinal cord and roots. Inflammation and demyelination were dose dependent and the caudal parts of the spinal cord were more affected than the cranial parts. The peripheral nerves were free of electrophysiological and morphological alterations. Systemic treatment with 4-aminopyridine accelerated and partially restored conduction in the dorsal columns and roots, while increasing the body temperature had a detrimental effect, suggesting demyelination as a prominent pathophysiological mechanism. These findings show that in AT-EAE in Lewis rats the dysfunction of the central nervous system and of spinal roots is cell dose dependent, that the peripheral nervous system distal to the spinal roots is spared, and suggest that paranodal demyelination is an important pathogenic mechanism.

INTRODUCTION

Experimental autoimmune encephalomyelitis (EAE) can be induced actively by immunization of animals with central nervous system (CNS) homogenates, CNS myelin, myelin basic protein (MBP) (for review, *see* Raine, 1985) or proteolipid protein (PLP) (Cambi *et al.*, 1983). Adoptive transfer has been achieved by inoculation of naive recipients with MBP (Ben-Nun *et al.*, 1981) and PLP (Satoh

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et al., 1987) specific T line cells with a helper/inducer phenotype, establishing the pivotal role of T lymphocytes in the pathogenesis of the disease. EAE induced by CNS tissue has been widely studied as a possible animal model of multiple sclerosis (MS) (Lassmann, 1983; Raine, 1984). EAE in the guinea pig, especially strain 13, has striking clinical and pathological similarities to MS (Raine and Traugott, 1984; Lassmann and Vass, 1987). The model disease in the rat gains its importance from a large battery of immunological probes available. In recent years the immunopathology of adoptive transfer EAE (AT-EAE) in the Lewis rat has been studied extensively (Cohen, 1984; Wekerle *et al.*, 1986) while comparatively little attention has been paid to the pathology and electrophysiology. This is surprising since the cause of the neurological deficits is not clear (Simmons *et al.*, 1982). Using electrophysiological techniques, Pender and Sears (1982, 1984) accounted for virtually all of the clinical signs of EAE in the rabbit to conduction block due to demyelination in the dorsal root ganglia and root entry axons, notwithstanding the functional abnormalities which might be associated with the central inflammatory or demyelinating lesions in the CNS, whose effects would be masked by the signs of the radiculopathy. In EAE of the Lewis rat demyelination in the ventral root exit zone may be the most important site of dysfunction (Pender, 1986; Pender and Sears, 1986). In the present study we investigated the pathophysiology of the functional defects in the CNS and in the peripheral nervous system (PNS) in AT-EAE using electrophysiological techniques that were developed for the study of experimental autoimmune neuritis (EAN) and adoptive transfer EAN (AT-EAN) (Heininger *et al.*, 1986, 1988; Hartung *et al.*, 1988*b*). We present data indicating that the cell dose dependent functional deficit in AT-EAE is best explained by paranodal demyelination in the CNS and the spinal roots.

MATERIAL AND METHODS

Animals

Inbred female Lewis rats (body weight 180-200 g, 8-10 wks old) were obtained from the Zentralinstitut für Versuchstierzucht (Hannover, West Germany).

MBP-specific T cell line and induction of EAE

The MBP-specific T cell line was established according to procedures described previously (Ben-Nun *et al.*, 1981; Fierz *et al.*, 1985). In brief, Lewis rats were sensitized with guinea pig MBP in complete Freund's adjuvant. After 10 days the draining lymph node lymphocytes were isolated and repetitively stimulated in the presence of MBP and irradiated syngeneic thymus cells. Between stimulations the cell line was expanded by incubation in interleukin 2-containing medium. A dose of 1×10^6 (lower cell dose group) or 5×10^6 (higher cell dose group) of freshly activated T cells was injected into the tail vein of naive recipient Lewis rats. Different batches of the same cell line were used for the experiments: higher cell dose group, lower cell dose group, 4-aminopyridine treatment, and effect of temperature. Control animals received 10^7 irradiated (3000 rad) MBP-specific T cells. Animals were scored clinically for AT-EAE using the following scale: 1, limp tail; 2, paraparesis; 3, tetraparesis; 4, moribund, death.

Electrophysiological testing

Measurements were carried out under general anaesthesia essentially as described in detail previously (Heininger *et al.*, 1986) with a Medelec MS 91b electromyograph. Central conduction was assessed by cervical and lumbar somatosensory evoked potentials (SEPs) recorded either at C7 or at T13/L1 after 100 stimuli to the tibial nerve at the left medial malleolus. The cervical SEPs were recorded with the active needle electrode at C7 (vertebra prominens) and the reference needle electrode at the forebrain above the base of the nose. The needle ground electrode was inserted subcutaneously at the quadriceps muscle. For convenience these SEPs were termed cervical SEPs though we are aware that the main component, a negative potential with a normal latency around 10 ms (N10) is generated by unidentified CNS structures. This arrangement was chosen since it delivered potentials with high amplitudes and good reproducibility in day-to-day measurements (variation coefficient of 3% for latencies and 15% for amplitudes), avoiding electrode implantation. In the lumbar SEP, the origin of the first positive deflection and of the R response, a small negative deflection superimposed on the rising phase of the S response, was determined by laminectomy at the third lumbar vertebra and transection of the spinal cord at the L4 level. Both components of the lumbar SEP were preserved in these rats while the S response was completely absent (Wehling *et al.*, 1988). To exclude the possibility that SEPs at C7 and L1 might be volume-conducted artefacts from distinct muscle contractions we recorded under succinylcholine-relaxation and mechanical ventilation in 2 rats. Waveform and amplitudes were essentially unchanged under neuromuscular blockade. Measurements of peripheral conduction at the left sciatic nerve included motor and mixed nerve conduction velocities (NVC), amplitudes of distally and proximally elicited compound muscle action potentials (CMAP), and latencies of H reflexes and F waves. The F waves were readily elicited in the plantar lateral flexor muscle after supramaximal stimulation of the tibial nerve at the ankle. Reproducible H reflexes in the plantar flexor muscles were only obtained after stimulation of the sciatic nerve at the sciatic notch just below threshold for the orthodromic motor response. Stimulation of the tibial nerve at the ankle gave inconsistent H responses.

Groups of 6 animals were examined 1 day before adoptive transfer and on days 3 and 4 (higher cell dose group) or on days 5, 7, 9, 12, and 17 (lower cell dose group) postadoptive immunization (p.i.) with T cells. Body temperature was measured with a rectal thermistor and maintained at 36±0.5° C with a warming lamp. The diseased higher dose group animals exhibited a marked hypothermia under room temperatures (around 22° C) and died on warming up in a pilot experiment. Therefore the higher cell dose rats were later examined at their low individual body temperature. To estimate the contribution of low temperature to the pathological electrophysiological findings, 5 normal female Lewis rats, matched for age and body weight, were examined electrophysiologically before and after being cooled down to similar low body temperatures by placing them on an iced cushion. The electrophysiological measurements could not be carried out blindly because even when anaesthetized the diseased animals were clearly distinguishable from the normal ones by the hypothermia, rough hair, conjunctivitis, scoliosis, and incontinence.

Effect of 4-aminopyridine and temperature

In 8 additional animals injected with the higher cell dose the effect of 4-aminopyridine (4-AP, Sigma, München, West Germany) and of changes in body temperature on the neural dysfunction was studied on day 4 or 5. Three of these rats were examined before and after intraperitoneal (i.p.) injection of 1 ml of physiological saline containing 0.2 mg of 4-AP, a reversible blocker of potassium channels (Yeh *et al.*, 1976). In the remaining 5 rats with AT-EAE-related hypothermia the effect of warming with a heating lamp was monitored electrophysiologically, 2 of these animals receiving an additional injection of 0.2 mg 4-AP. To control for effects of 4-AP unrelated to the pathological changes, 2 normal rats at a body temperature of 36° C and 2 normal rats after being cooled to 29° C were injected with 0.2 mg and 1 mg of 4-AP and the changes examined electrophysiologically.

Morphological examination

To keep the animals available for electrophysiological evaluation at a constant number throughout the study, for morphological examination 6 additional rats from the same litter were injected with the lower cell dose and monitored electrophysiologically until killing. On day 5 (6 higher and 2 lower cell dose rats) and on days 6 and 8 p.i. (2 lower cell dose rats each) animals were anaesthetized, perfused and specimens prepared for light microscopy as described previously (Heininger *et al.*, 1988). Transverse and longitudinal sections (1 μm) from the brain, different levels of the spinal cord, cauda equina, and right sciatic nerve were evaluated blindly.

RESULTS

Clinical course of AT-EAE

The first clinical signs were seen 4 days after intravenous injection of either 1×10^6 or 5×10^6 MBP-specific T line cells. On day 4, animals receiving the higher cell dose of 5×10^6 cells developed a fulminant tetraplegia, marked hypothermia (28-30° C), irritability, and epileptic seizures (clinical score 3-4) and died on day 5 p.i. (fig. 2).

Rats injected with the lower cell dose exhibited a limp tail and hind limb weakness on day 5 p.i. Maximal clinical illness was observed between days 5 and 7 with hindlimb paraplegia in only some animals (mean clinical score 2), followed by gradual improvement with complete remission at 3 weeks p.i. (fig. 3).

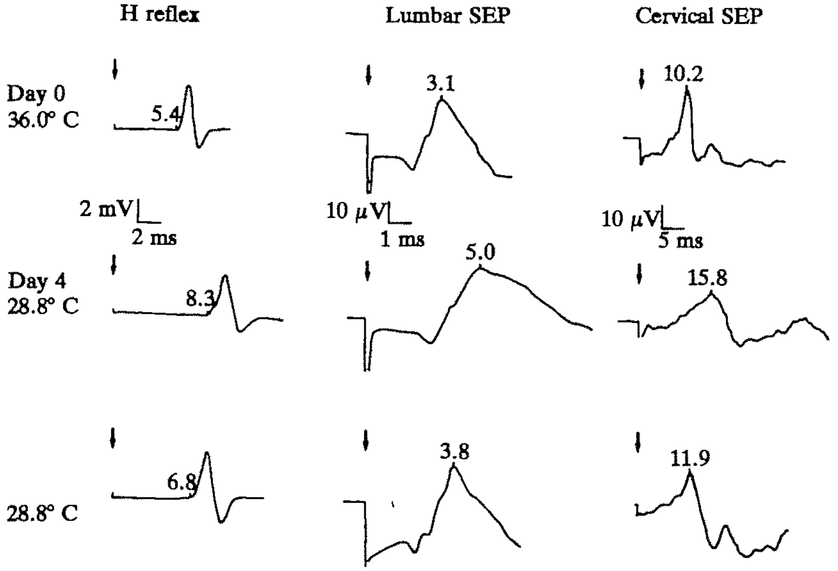

FIG. 1. Redrawn representative original recordings of H reflex, lumbar SEP, and cervical SEP before (day 0) and after (day 4) adoptive transfer of 5×10^6 MBP-specific T line cells. The *bottom line* represents potentials of a normal control examined at a low body temperature of 28.8° C, the body temperature at which the higher dose animal was measured on day 4. For these and all other recordings, negativity at the active electrode is represented by an upward deflection. Here and in figs 4, 5, and 6 latencies to the first negative deflection (M waves, F waves, and H reflexes) and to the peak of the main negative component (SEPs) are indicated and given in milliseconds. Note the different amplitude and time scales.

Control rats injected with 10^7 irradiated MBP-specific T cells did not exhibit clinical signs.

Electrophysiological findings

Animals injected with 5×10^6 T cells were completely normal until day 4 when a marked slowing of conduction in the dorsal columns and in the roots was observed in all diseased rats (fig. 1). The main component of the cervical SEP (N10) was delayed by 32% of temperature-matched control values (percentage of changes is given as a mean of 6 animals throughout in comparison with temperature-matched normal rats) with an increased temporal dispersion (figs 1, 2). The lumbar SEP showed a delay of the initial positive deflection and of the R wave (conduction distal to the spinal cord) and of the S response (dorsal column conduction, delay of 34%) (fig. 1). Latencies of H reflexes and F waves were prolonged by 23%, temporal dispersion was not a consistent finding. The peripheral NCVs of the diseased animals and the temperature-matched normal animals did not differ. The amplitudes of cervical SEPs were slightly reduced while the amplitudes of CMAPs were virtually unchanged.

In the lower cell dose group which exhibited a minor hypothermia with values around 32–34° C warming to 36° C was well tolerated. In this group the

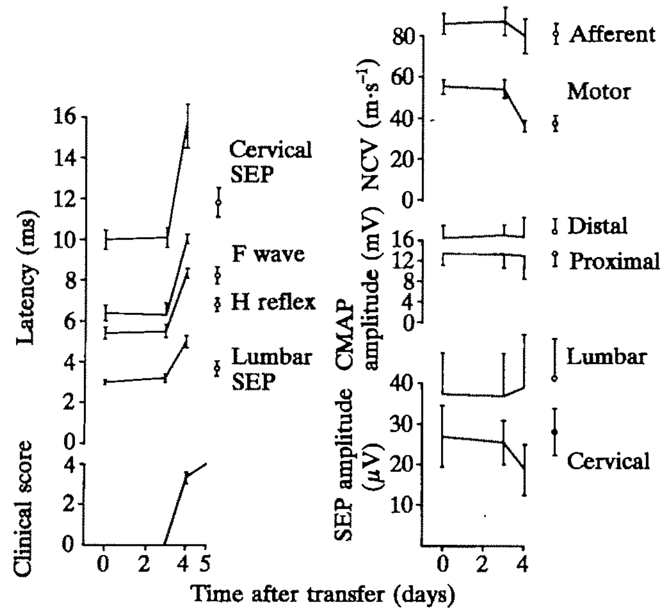

FIG. 2. Time course of clinical signs and electrophysiological findings in Lewis rats injected with 5×10^6 MBP-specific T line cells (higher dose). Mean values of 6 recipient rats (±SD) are given. *Left panel* from top to bottom: latencies of cervical SEPs (N10), F wave, H reflex, S response, and clinical score. *Right panel* from top to bottom: mixed NCV, motor NCV, CMAP amplitudes, amplitudes of lumbar S response, amplitudes of cervical SEP (N10). The values ±SD obtained from temperature-matched controls to evaluate the contribution of hypothermia to the pathological findings are represented by open circles to the right of the respective curve.

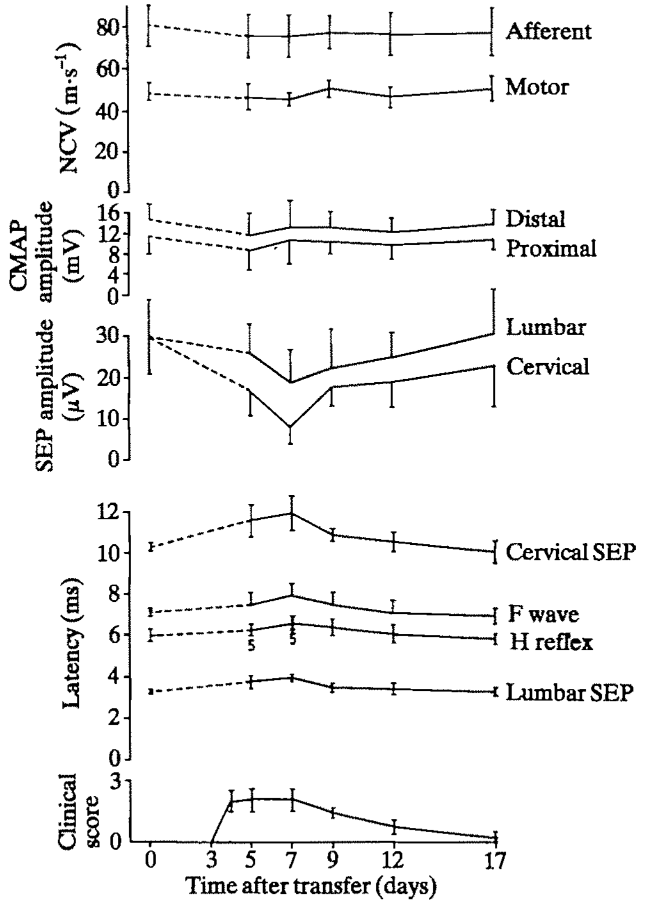

FIG. 3. Time course of clinical signs and electrophysiological findings in rats injected with 1 × 10^6 MBP-specific T line cells (lower dose). Mean values of 6 recipient rats (±SD) are given. From top to bottom: mixed NCV, motor NCV, CMAP amplitudes, amplitudes of lumbar S response and cervical SEP (N10), latencies of cervical SEPs (N10), F wave, H reflex, lumbar S response, and clinical score; 5 denotes that H reflexes were obtained only in 5 of the 6 rats.

progression of functional deficit was more gradual, the delay of latencies was less pronounced and the highest degree of abnormality was attained only on day 7 p.i. At that time the latencies of cervical N10 and lumbar S response were prolonged by 16% compared with pretreatment values. The amplitude of the N10 response was reduced by 75%, the S response by 40% (fig. 3). The latencies of H reflexes and F waves were delayed by 10 and 11%, respectively, these potentials also showed a loss in amplitude. In one of the 6 animals the H reflex could no longer be elicited. These abnormalities gradually remitted over the next 10 days, reaching normal values by day 17 p.i. The motor and mixed afferent NCVs and potential amplitudes of the sciatic nerve were unchanged throughout the course of the disease in the lower dose animals.

Control rats receiving 10^7 irradiated T line cells did not exhibit any electrophysiological changes.

Effect of treatment with 4-aminopyridine

Fifteen minutes after intraperitoneal injection of 0.2 mg 4-AP in 3 higher dose animals on day 4 (body temperature 28–30° C) the abnormally prolonged latencies of cervical and lumbar SEPs were shortened by a mean of 31%, latencies of H reflexes and F waves improved by 15% (fig. 4) and became near normal when compared with the values in temperature-matched controls. Peripheral nerve conduction was not altered after 4-AP. Further monitoring of 4-AP-induced electrophysiological changes was hampered by excessive motor activity due to 4-AP-evoked seizures.

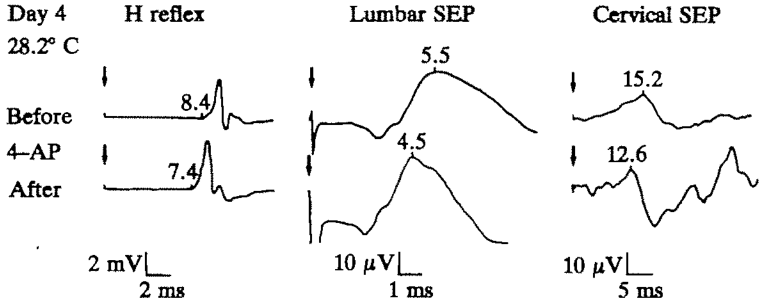

FIG. 4. H reflex, lumbar SEP, and cervical SEP of a higher cell dose AT-EAE rat on day 4, before and 15 min after injection of 0.2 mg 4-aminopyridine (4-AP). Note the different amplitude and time scales.

Treatment of 2 normal rats with 0.2 mg of 4-AP at either 36 or 29° C did not change the electrophysiological findings compared with pretreatment values. In contrast, i.p. injection of 1 mg of 4-AP in 2 normal rats at 36° C resulted in a striking enlargement of potential amplitudes of cervical N10 to about twice the starting value. At 29° C the effects of 1 mg 4-AP were attenuated to an increase of N10 amplitude of 50%, latencies remained virtually unchanged. However, further electrophysiological monitoring in all the animals receiving a dose of 1 mg 4-AP was rendered impossible by the advent of epileptic seizures.

Effect of temperature

The effect of temperature was assessed in another group of 5 higher dose animals on day 5. The disease-related hypothermia ranged from 25.3 to 29.4° C. In all rats, increasing the body temperature resulted first in a gradual speeding up of central and peripheral conduction with shortened latencies while the amplitudes of H reflexes, F waves and SEPs were slightly reduced (fig. 5). This effect was observed 2–3° C above the starting temperature. Then, with a further rise of 2–3° C, a marked loss of amplitudes of SEPs, H reflexes and F waves ensued.

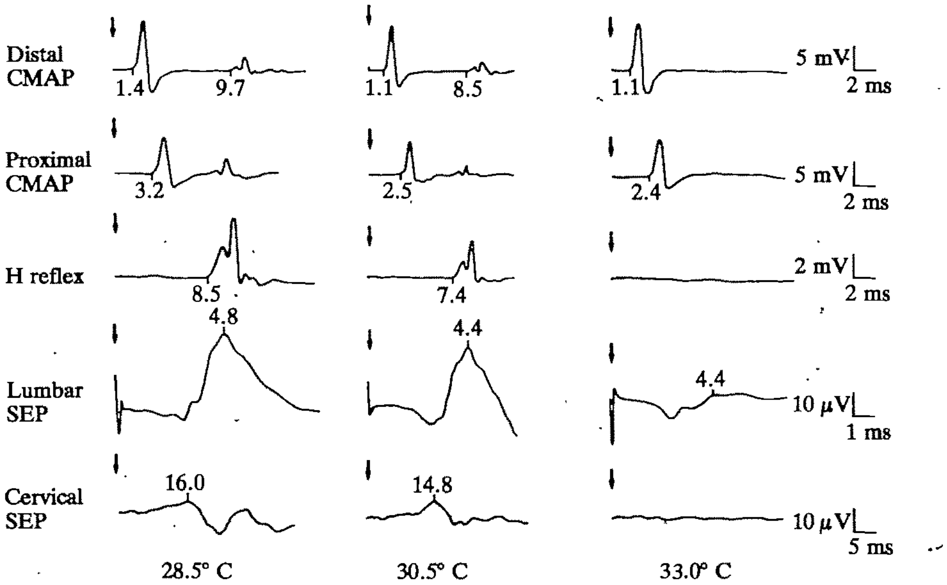

FIG. 5. Effect of raising the body temperature on distal and proximal compound muscle action potentials (CMAP), H reflex, lumbar SEP, and cervical SEP in a higher dose AT-EAE rat on day 5. Note the different amplitude and time scales.

Interestingly, in 2 rats the R wave of lumbar SEP could still be elicited although the S response was almost lost. The latencies remained virtually unchanged during this phase. Finally, all electrical activity of central pathways ceased and the animals died shortly thereafter. Peripheral conduction was virtually unaltered during this phase until death, and NCVs and amplitudes were in the range of normal temperature-matched controls. These events occurred in the individual animals within approximately 6° C above the starting temperature and appeared to be independent of the absolute body temperature.

Combined effects of changes in body temperature and of 4-amino-pyridine treatment

The combined effects of temperature and 4-AP on the cervical SEP were monitored in 2 higher dose rats on day 5. In 1 animal the initial potential with a latency of 19.2 ms at 25.8° C gradually waned on warming to 32° C to a hardly detectable baseline deflection with a latency around 17 ms. After injection of 0.2 mg 4-AP the latency shortened dramatically to 10.0 ms, regaining about 50% of the initial amplitude (fig. 6). In the other animals 4-AP also induced a shift of the N10 potential from 15.0 ms to normal values but the temperature-dependent conduction block could not be reversed (initial amplitude of 24 μV at 28.7° C, amplitudes at 31° C 6 μV before and 5 μV after 4-AP, respectively).

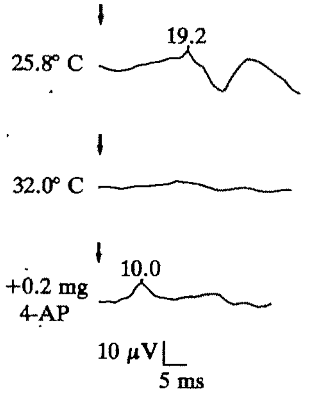

FIG. 6. Combined effects of raising the body temperature and treatment with 0.2 mg 4-AP on cervical SEP of a higher dose AT-EAE rat on day 5.

Histological findings

The morphological hallmark in AT-EAE Lewis rats was a dose-dependent marked inflammation with infiltration of mononuclear cells throughout the CNS, especially in the brainstem and spinal cord, but also in the ventral and dorsal roots. The spinal root entry and exit zones were predominantly affected. Inflammation and oedema was most prominent around vessels in the Virchow-Robin space, with perivascular cuffing (fig. 7). In the higher dose animals a diffuse parenchymal infiltration of inflammatory cells was seen as a consequence of confluent perivascular lesions, especially in the subpial region. There was also widespread infiltration of mononuclear cells between the meningeal sheaths. Inflammatory cells were

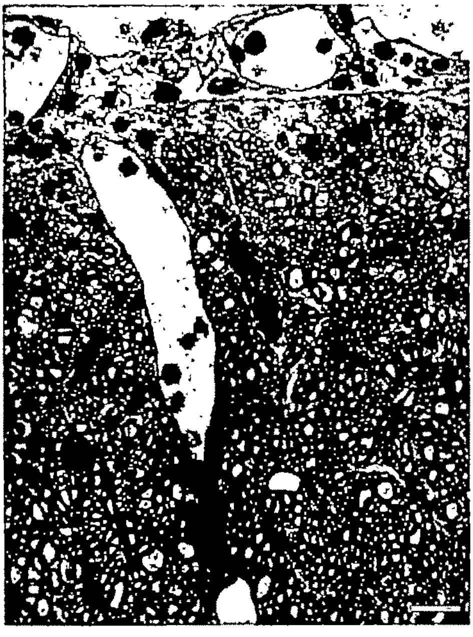

FIG. 7. Transverse section through the lumbar spinal cord of a higher dose AT-EAE rat on day 5 p.i. There is extensive perivascular as well as meningeal and subpial infiltration of mononuclear cells. Inflammatory cells are found adherent to the luminal side of the endothelium. Bar = 50 μm.

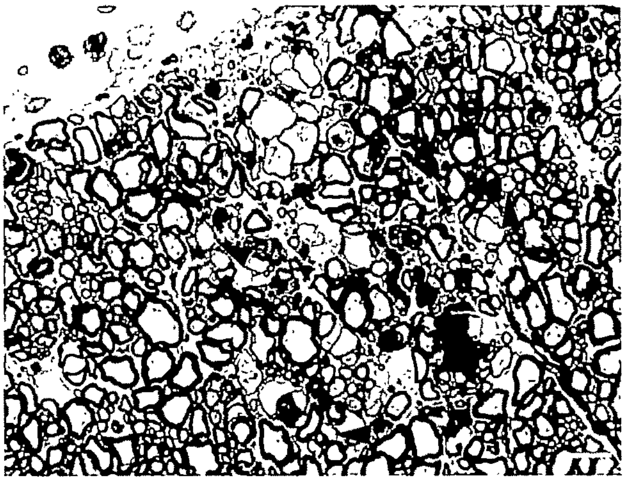

FIG. 8. Transverse section through the lumbar spinal cord of a higher dose AT-EAE rat on day 5 p.i. showing subpial lesion with tissue infiltration by mononuclear cells, demyelinated axons (arrowheads), splitting of myelin sheaths, myelin debris and several axon spheroids (arrow). Bar = 20 μm.

often found adherent to the luminal side of the endothelium of otherwise empty and perfused vessels (fig. 7). These histological abnormalities were less pronounced and appeared later in the lower dose animals. Sequential transverse sections at defined 1 cm distances along the spinal cord showed that the inflammation was more prominent at the caudal parts.

In the higher dose animals, in regions of intense inflammation, selective primary demyelination with splitting of myelin sheaths and denuded axons was observed alongside axonal degeneration and myelin breakdown. Myelin debris was ingested by macrophages (fig. 8). Longitudinal sections of the spinal cord did not reveal any definite paranodal myelin alterations.

In transverse and longitudinal sections of the roots, cauda equina and dorsal root ganglia of higher dose animals, occasional perivascular infiltration of inflammatory cells and myelin splitting was also present. Here interstitial oedema was a prominent feature and was detected by an increased interneuronal distance. Sciatic nerve sections showed no abnormalities.

Rats injected with 10^7 irradiated T cells were histologically normal.

DISCUSSION

EAE can be induced in naive Lewis rats by adoptive transfer of MBP-specific T line cells (Ben-Nun *et al.*, 1981). The present study was undertaken to examine the course and pathophysiology of functional deficits in the central and peripheral nervous system of AT-EAE by electrophysiological methods.

Onset, course, and severity of electrophysiological changes correlated with clinical and histological findings and were dependent on the number of MBP-specific T cells transferred. Rats injected with the higher cell dose exhibited a fulminant tetraplegia paralleled by slowing of conduction that was severe in the CNS and moderate across the root level with only minor reductions of amplitudes. In the lower dose animals, the clinical and electrophysiological abnormalities developed more gradually, were moderate, and returned to normal values within 3 weeks. Latencies of SEPs, H reflexes, and F waves were less prolonged than in the higher cell dose group, but there was a conspicuous reduction of potential amplitudes.

The pathophysiology of impaired conduction has been analysed in various ways. Increasing body temperature in diseased animals had a detrimental effect on central conduction with a reduction of amplitudes, while 4-AP accelerated and partially restored central conduction by shortening latencies and enlarging potential amplitudes. It has long been known that raising the body temperature induces a reversible conduction block in demyelinated nerve fibres (Davis and Jacobson, 1971; Rasminsky, 1973). On the other hand, cooling restores conduction in demyelinated fibres by prolonging the duration of action potentials by retarding Na^+ inactivation and slowing of K^+ conductance (Schauf and Davis, 1974). Similarly, drug-induced inhibition of Na^+ channel inactivation and/or of K^+ channel activation can restore conduction in previously blocked nerve fibres (Schauf and Davis, 1974; Bostock and Sears, 1978). One such drug is the K^+ channel blocker 4-AP (Yeh *et al.*, 1976) which improves conduction in experimentally demyelinated fibres (Sherratt *et al.*, 1980; Bostock *et al.*, 1981). Propagation of a nerve impulse is often blocked or profoundly slowed at the junction between the normal region and the demyelinated segment (Rasminsky and Sears, 1972; Waxman, 1978) as a consequence of capacitative and resistive shunting (for review, *see* Kocsis and Waxman, 1985). The conduction block at this site can be reversed by prolonging the action potential through blockade of voltage-dependent potassium conductance. Because internodal K^+ channels are normally covered by the myelin sheath (Chiu and Ritchie, 1980), 4-AP can only act on demyelinated axons where these channels are exposed (Bostock *et al.*, 1981). Consequently, the effects of temperature and of 4-AP in our experiments are best explained by paranodal, and possibly segmental demyelination, as a prominent pathogenetic mechanism in AT-EAE. Because hypothermia and 4-AP have different mechanisms of action affecting predominantly Na^+ inactivation and K^+ activation, respectively, both mechanisms can be additive. This then may result in a greater improvement of conduction than brought about either by hypothermia or 4-AP alone.

Histologically, segmental demyelination and myelin splitting was a less prominent feature than inflammation and oedema. Paranodal changes, however, may escape from light microscopic detection, even in longitudinal sections, and may only be seen by histochemical methods at the electron microscopical level (Waxman and Quick, 1977; Weiner *et al.*, 1980). Studies to examine this are in progress.

Another mode of action of 4-AP is an improved ability of conducting repetitive impulse activity in partially demyelinated fibres. This is an unlikely possibility at the comparatively low rate of stimulation used in the present study (1 Hz). At physiological firing rates this may be an important mechanism and could account for clinical benefit of 4-AP in MS patients (Stefoski *et al.*, 1987). As the animals were anaesthetized, the clinical effects of 4-AP could not be assessed.

In addition to effects on demyelinated fibres 4-AP treatment may lead to improved synaptic transmission by effects on peripheral (Lundh *et al.*, 1977, 1979) and central synapses (Rutecki *et al.*, 1987). Indeed, a high dose of 4-AP (1 mg) given to normal rats resulted in a potentiation of conduction, suggesting synaptic effects; a dose of 0.2 mg 4-AP did not. However, in AT-EAE and EAE the blood-brain barrier is profoundly damaged (Vulpe *et al.*, 1960), with the possible consequence that 4-AP may enter the brain parenchyma more easily and in higher concentration than in normal animals. Moreover, there may be an increased synaptic sensitivity in diseased animals to 4-AP. It therefore cannot be ruled out that a part of the gain in amplitude induced by 4-AP is due to synaptic effects, even with a dose of 0.2 mg.

It has previously been suggested that axonal dysfunction in faster conducting fibres following inflammatory oedema may contribute to the deficits in EAE and AT-EAE (Simmons *et al.*, 1984; Wekerle *et al.*, 1986; Paterson, 1987). Our findings do not support this assumption. In animals given the higher cell dose, the effects of 4-AP and temperature argue against irreversible axonal damage as a prominent feature. In rats with the lower cell dose, however, a conspicuous loss of amplitudes was apparent. Some part of this obvious difference between higher and lower cell dose animals can be attributed to the fact that those given the lower dose were examined electrophysiologically at 36° C after previously raising the body temperature. As we have seen with the higher cell dose, this may, in itself, have reduced the potential amplitudes. Another factor may be preferential damage to smaller, slowly conducting fibres in the lower cell dose rats, leaving faster conducting fibres relatively intact. Preferential dysfunction of smaller diameter myelinated fibres was observed in active EAE (Pender, 1986, 1988), and was also a feature of demyelination of rat spinal root fibres induced by antigalactocerebroside antibody (Lafontaine *et al.*, 1982). Whatever mechanism applies, it appears that delay of latencies and reduction in amplitudes traditionally ascribed to demyelination and axonal dysfunction, respectively, may not be different and unrelated phenomena but consequences of the same noxious mechanism in CNS inflammation.

The principal site of nerve dysfunction and nerve damage in AT-EAE is the CNS, especially the spinal cord, although involvement of the spinal roots and ganglia may be an equally important cause of the functional defect. We found widespread perivascular inflammation (*see* Wekerle, 1984), predominantly subpial and similar to a previous report (Matsumoto and Fujiwara, 1987) and this was paralleled by profound slowing of conduction along the spinal neuraxis.

Histologically, as in EAE (Pender and Sears, 1986), the caudal segments of the spinal cord and adjacent roots were more affected than the cranial parts, and the dorsal root entry and the ventral root exit zones were sites of predilection for nerve damage. Electrophysiologically, Pender (1986) recently showed by direct recordings that the lumbar ventral root exit zone is a major site of conduction block while conduction through the dorsal root entry zone was normal, suggesting that the afferent pathway to the spinal cord did not contribute significantly to the hindlimb motor dysfunction in EAE. In contrast, another study showed a clearly demonstrable conduction block of large afferent fibres in the dorsal root ganglia contributing, presumably, to the ataxia (Pender and Sears, 1986). In AT-EAE the dorsal roots may contribute to the neurological deficit as demonstrated by the delayed R wave of the lumbar SEP. The preserved R wave, in conjunction with the almost complete loss of the S response during warming, provides evidence that the roots are affected less severely than the spinal cord. The equal delay of F waves and H reflexes further suggests that the ventral and dorsal roots are similarly involved in AT-EAE. Electrophysiological and histological examination of the distal PNS did not reveal any involvement in the pathological process.

The mechanisms by which MBP-specific T cells induce AT-EAE are not completely understood. A secondary recruitment of host immunoinflammatory factors including cytotoxic T cells, macrophages (Heininger *et al.*, 1988), complement (Vanguri *et al.*, 1982), eicosanoids (Hartung *et al.*, 1988*b*), lymphokines (Brosnan *et al.*, 1988), vasoactive amines (Johnson *et al.*, 1988), and oxygen radicals (Hartung *et al.*, 1988*c*), or a direct cytotoxic attack of the T line cells (Yarom *et al.*, 1983; Sun and Wekerle, 1986) have been proposed (reviewed by Hartung *et al.*, 1988*a*). In addition, antimyelin antibodies may be produced or naturally present (Stefansson *et al.*, 1985) and cause damage (Fierz *et al.*, 1988; Linington *et al.*, 1988). Further analysis of the principal factors causing the functional deficits described here may lead to a better understanding of the pathophysiology of human demyelinating disease and offer new strategies for pharmacological intervention.

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BOOK REVIEWS

Charcot, the Clinician: the Tuesday Lectures. Translated with commentary by C. G. Goetz. 1987. Pp. 223. New York; Raven Press. Price $67.50.

When Charcot died in 1893, the everyday practice of neurology was unrecognizable by comparison with the discipline he had been exposed to as a student in the 1840s. Charcot brought a new approach to old problems and so did for neurology what William Webb Ellis had done for the football. Influential pupils and acquaintances spoke and wrote so well of him, during and after his life, that posterity has had no hesitation in placing Charcot on one of its loftiest pedestals where he remains, perfectly balanced.

The documentation of Charcot's methods and the details of his discoveries in clinical neurology are to be found in five volumes of lectures on neurological disease, published in English by the New Sydenham Society between 1877–1899, very many copies of which survive; despite Charcot's assistance, the lectures must have altered in the process of editing (by Drs Borneville and Brissaud) and translation (by Drs Sigerson, Savill, Tuke and Hadden). Less easy to locate are accounts of the clinical demonstrations which provided source material for these published lectures. 'Leçons du Mardi', which appeared in 1892 is not well known and has never been republished or translated in its entirety. There also exists, in the Charcot Library at the Salpêtrière, an earlier copy of handwritten lecture transcriptions to which Dr Goetz had access whilst on a visit to Paris and which forms the basis for his translations with commentary of 9 cases selected to illustrate Charcot as teacher and practitioner.

In the first demonstration, Charcot presents a case of neurosyphilis; this is neurology 'on the hoof' for although Charcot knows the case well he must steer the patient's responses in such a way as to ensure that the clinical lessons are well learned. The dialogue and map which illustrates the route followed by Charcot's second case during his absences bristle with atmosphere. Does a faint whiff of garlic not rise from the page as the 37-year-old delivery man describes to the audience in the Tuesday clinic, meandering down the Rue Amelot during one of his five amnestic episodes? Charcot quotes extensively from Macbeth in formulating his opinion on the epileptic nature of these fugues. Case 3 poses problems for, in seeking not to provide scatological offence to his nineteenth century audience, Charcot goes to elaborate circumlocutory lengths in describing the coprolalia characterizing a case of Gilles de la Tourette syndrome. Next, the Professor presents cases of Sydenham's chorea and Huntington disease and, after lengthy interviews supplemented by a historical account, he concludes that these are variants of the same disease; in this and the later presentation of Friedreich's ataxia Charcot demonstrates clearly the value of taking an extended family history and of being critical in its interpretation. This little anthology of cases would be incomplete without an example of hysteria; Charcot defends himself against the suggestion that hysteroepilepsy was no more than an artefact arising from the cohabitation in the Salpêtrière of epileptics and hysterics; Dr Goetz reminds us that on her deathbed the most famous hysteroepileptic of all—Blanche Wittman, model for the Brouillet painting 'A clinical Lesson at the Salpêtrière'—whose condition improved smartly following cessation of Charcot's demonstrations, resolutely maintained her innocence whilst in the same breath shopping several notorious fakes of her acquaintance. Dr Goetz includes a case of Parkinson's disease mostly to highlight the role of art in Charcot's work; he drew some of the evocative illustrations with which work at the Salpêtrière of this period is associated but was much assisted in this by his colleague Paul Richer. In the last case demonstration Charcot describes amyotrophic lateral sclerosis, detailing the emotional release, glossolabial laryngeal paralysis and fasciculations; he notes the universally poor prognosis but anticipates that perceptions of the disease will change with emergence of its true clinical spectrum.

The clinical descriptions are accompanied by Dr Goetz's commentaries; these are sometimes used to apply a modern interpretation on the cases but he chooses not to contest many diagnoses. Occasionally he wanders somewhat from the matter in hand—as in the discussion of Charcot, Dreyfus, Proust and antisemitism—and there is some padding, but in general these commentaries serve as a useful vehicle for describing life and people at the Salpêtrière. Moreover, they provide a backdrop for the excellent pictures; anyone wanting to illustrate lectures with drawings of the fabric or inmates of the Salpêtrière, many taken from the Nouvelle Iconographie de la Salpêtrière, will want access to this book. But the translation is sometimes awkward. Is it correct to record Charcot as commenting that a music teacher was 'fired' for undressing in front of a female patient (allegedly not in admiration but during an epileptic fugue)? Someone at Raven Press has not checked the proofs very carefully and there is 'economy with accuracy' on the grand scale. Charcot would have had difficulty in giving a lecture on October 23, 1988 and the English community would not have had the prescience to designate tabetic arthropathy as Charcot's joint disease in 1812; Romberg's Manual of Nervous Diseases was not published by the New Sydenham Society; Tyson (1650–1708) was not physician to the Bethlehem Hospital; Gowers' Manual of Diseases of the Nervous System was not published in 1983—and so on. Barely a page escapes these minor irritations which in the end seriously detract from the pleasure of Charcot's company.

Dr Goetz has drawn attention to an important historical document; it is to be hoped that an enlarged and definitive edition of Charcot's 'Leçons du Mardi' will follow.

D. A. S. COMPSTON

Embodiments of the Mind. By Warren S. McCulloch. Introduction by Seymour Papert. New foreword by Jerome Y. Lettvin. 1988. Pp. 402. London: MIT Press. Price £11.25.

This reissue of essays and poems, first collected in 1956, may stimulate us to ask how far we have gone towards the synthesis that Warren sought. He hoped to provide the foundations of an empirical epistemology but, as Jerry Lettvin puts it in his foreword 'There is still no theory to give coherence to this mountain of data in terms of how the brain functions as a mechanism that sustains mental process'. McCulloch and Pitts hoped that they had taken a step towards such a theory in their paper of 1943: 'A logical calculus of the ideas immanent in nervous activity'. They based their system on the concept of a threshold neuron subject to excitation and inhibition, the response being 'factually equivalent to a proposition which proposed its adequate stimulus'. This idea they developed with an intimidating array of mathematics, the forerunner of a host of theories that have proved to be of little or no help to actual students of the brain.

It is easy to dismiss McCulloch and Pitts' theory as simple minded but it opened a new field by the arrogant presumption of its suggestion that there must be a class of computable functions that define the behaviour of a brain. It is interesting that in the same year (1943) another seminal paper was published, by Bigelow, Rosenblueth and Wiener, on the principle of mechanisms that show purpose. These two papers together provided the basis for the development of cybernetics and artificial intelligence. They have the common feature of 'recognition that the laws governing the embodiment of mind should be sought among the laws governing information rather than energy or matter', as Papert puts it in his introduction.

McCulloch was indeed an innovator and a teacher. He was an unforgettable person, large in every sense; as Lettvin says, he had something of the character of a cavalier. He was generous of his time, but he expected you to follow his thoughts, which was not always easy. He was trained as a mathematician and logician and his writing, like his speech, is often abstruse and allusive, but also arresting and memorable. He was full of useful knowledge, good sense and personal observation; one feels that one learns something on every page.

The article that for this reviewer best summarizes his influence is 'What the frog's eye tells the frog's brain'. This famous paper, written in 1959 with Pitts, Lettvin and Maturana, consciously represented a first essay in experimental epistemology. It puts forward an 'initial argument' which is essentially that if we are to discover how the nervous system works we must go beyond the simple physical principles that had previously governed the choice of experiment by biophysicists. As they put it 'the laws found by using small spots of light on the retina may be true and yet, in a sense, be misleading'. What the authors did was to find the response of optic nerve fibres of a frog 'not only (to) spots of light but (to) things he would be disposed to eat . . .'. And of course they found that 'the eye speaks to the brain in a language already highly organised and interpreted, instead of transmitting some more or less accurate copy of the distribution of light on the receptors'. For example 'bug perceivers . . . respond best when a (small) dark object . . . enters the field, stops and moves about intermittently thereafter'. Thus the operations can be understood if we interpret their meaning in the life of the frog.

Of course the situation is very different in mammals, but it would be interesting to know what influences passed in 1957 and 1958 between McCulloch's group at MIT and Hubel and Wiesel in Harvard. Umberto Maturana was a young Chilean of a philosophic turn of mind, who had been studying the frog's eye at University College, London, before joining McCulloch. It may have been he who brought new ideas to the group. It is interesting that this article about the frog contains no mathematics or symbolic logic; but it shows, like all McCulloch's work, how a historical and theoretical approach should precede the choice of experiment. Reading these essays again reminds me of the excitement of those days. Much of what they say is still relevant today, when we know that neurons are not simple yes/no units and we can imitate them with devices much smaller than thermionic valves.

J. Z. YOUNG

Dystonia 2. *Advances in Neurology*, Volume 50. 1988. Edited by S. Fahn, C. D. Marsden and D. B. Calne. 1988, Pp. 731. New York: Raven Press. Price $122.50.

Dystonia 1 (Volume 14), published in 1976, kindled a new era of interest in this perplexing phenomenon, the embers of which have been unflaggingly inflamed by the promotional labours of a few dedicated aficionados and the advent of the first really effective palliative remedies. Most of the information contained in the first volume has now been widely disseminated throughout the neurological community, and a new encyclopaedia was needed. The present volume fulfils this demand and is a far more substantial affair than its now rather puny progenitor.

What advances have occurred in our understanding of dystonia in the last ten years? The classification has been refined and unified so that most clinicians now talk of idiopathic (primary) or symptomatic (secondary) types. Many of the idiopathic cases are autosomally inherited through a dominant gene and the more scrupulously one examines the relatives of probands the more frequently cryptic cases of focal dystonia and essential tremor are found. Bressman in this volume also challenges the view that Ashkenazim pedigrees are recessive, suggesting instead an autosomal dominant inheritance. The age of onset and distribution of the abnormal movements (focal, segmental, multifocal) are also important in classification. The large majority of patients with hemidystonia will prove to have a secondary cause, whereas the figure for generalized cases is about 50% and is down to 10% in the segmental and focal forms. The comprehensive investigation of a case of dystonia looking for specific causes is now a complex, expensive and generally unrewarding business. There are 8 identified biochemical defects which may be present with torsion dystonia, Wilson's disease and homocystinuria being the most important to pick up, as treatment may be offered. There are another 9 conditions which can be identified by a biological marker including Leigh's disease, Niemann-Pick type C, neuroacanthocytosis, ataxia telangiectasia and Kufs' disease. There are 14 causes of basal ganglia necrosis detectable on neuroimaging and occult perinatal damage and tumours may also be diagnosed on scans. Drugs, particularly neuroleptics, psychiatric causes and the Sandifer-Kinsbourne syndrome where abnormal neck movements are associated with a hiatus hernia are other conditions to be aware of.

I found the short chapter by Sucherowsky and Donald Calne on nondystonic causes of torticollis particularly helpful, having been caught out recently with a rotatory atlanto-axial subluxation in a young girl who to all the world looked as if she had a classical spasmodic torticollis. The clue to this diagnosis is the usually relatively sudden onset, the characteristic head posture (bird with head cocked listening for a worm) and its persistence during sleep. AP open mouth views of C1-C2 with 15° rotation views to each side and CT scanning are the crucial investigations. Other nondystonic causes of torticollis include neoplasms or infections of the cervical spine and nasopharyngeal lesions, posterior fossa tumours and eleventh cranial nerve tumours.

The use of small doses of botulinus toxin at approximately three-monthly intervals into the affected muscles is now the undisputed treatment of choice of blepharospasm. Results are less spectacular in spasmodic torticollis owing to the size and number of muscles involved, but nevertheless relief of pain almost always occurs and about 50% of patients gain a considerable improvement in neck posture. Injection of masseter and temporalis muscles for oromandibular spasms and the thyroarytenoid for spasmodic dysphonia are also proving promising. This technique, along with other existing drug and surgical therapies, is well covered.

The dystonias are an under-diagnosed group of neurological disorders and the advent of an effective treatment for many focal dystonias has confirmed what many of us suspected, that these conditions are far more common than was hitherto acknowledged. Despite obvious therapeutic gains the pathophysiology of dystonia remains obscure, although a recent postmortem study has emphasized the possible importance of noradrenaline dysfunction. The possibility that local peripheral trauma may be an important triggering factor in constitutionally predisposed individuals continues to be hotly debated, but successful compensation claims have already been won both here and in the United States. The possibility that lesions outside the basal ganglia may cause dystonia also continues to niggle uneasily. All these contentious issues and many more are illuminatingly discussed within this book. Its success is assured and the only speculation can be on how long it will last as the definitive tome for those who need to seek advice on the diagnosis or management of dystonia.

A. J. LEES

Neuromuscular Diseases. A Practical Approach to Diagnosis and Management. Second edition. By Michael Swash and Martin S. Schwartz. 1988. Pp. 456. London: Springer. Price £99.00.

This second edition, now appearing seven years after the first, reflects the impressive advances in knowledge that have taken place during this time. The length of this edition has been increased by one-half, and the number of references doubled. Both authors are clinical neurologists, Swash having a special interest in muscle and nerve pathology and Schwartz, in clinical neurophysiology. Their aim has been to write a book which provides in-depth coverage of virtually all aspects of neuromuscular disease. Such a comprehensive exposition is probably not covered in any other single volume, and is clearly the book's greatest attribute. There are large sections on clinical assessment, neurophysiological techniques, muscle and nerve biopsy, pathophysiological correlations and compensatory mechanisms, classification of neuromuscular disease and then sections providing detailed coverage of each disease. The coverage includes clinical, electrophysiological, pathological and biochemical features, methods of treatment, prognosis and research implications. The book ends with a miscellaneous chapter in which there are novel discussions on such diverse entities as the stiff-man syndrome and hysterical weakness.

The information is well organized and written in a clear, matter-of-fact style. Tables and figures are used without hesitation to amplify and clarify the text. For example, there is a figure to show the metabolic pathway for ATP synthesis in mitochondria, another to show the chief needle EMG changes in myotonic dystrophy and one to illustrate the histological appearance of cross-sections of normal human muscle.

The authors have usually met their goal of comprehensive coverage, but they have often failed to achieve in-depth coverage. As an electromyographer, I was particularly concerned about areas dealing with electrophysiology. In performing needle electromyographic examinations, Schwartz advocates holding the needle in the left hand, rather than the right. He advises against advancing the needle in short increments since it is, in his experience, unusually painful. By following this advice, the electromyographer may miss isolated areas of denervation, or the early evidence of denervation which is often manifest by a brief run of positive sharp waves following normal insertion activity. A figure of a nerve conduction study in the carpal tunnel syndrome suggests incorrect placement of surface recording electrodes over the thenar muscle. Another figure purports to show the typical repetitive nerve stimulation results in Lambert-Eaton syndrome; but shock artefact is excessive, there is again a problem with electrode placement, and uncertainty as to whether there is a diagnostic change in amplitude. In discussing acute neurogenic disorders, it is stated that motor unit firing rates may be normal or slightly reduced in anterior horn cell disorders, but the usual experience is that such firing rates are increased—a finding of considerable diagnostic importance when the differential diagnosis involves upper motor neuron conditions. Many of the figures designed to show clinical signs are excellent but others are unsatisfactory. For example, the photograph to show thenar wasting in the carpal tunnel syndrome is unconvincing. There may be similar concerns for those who have special knowledge in other disciplines.

Despite these weaknesses, the book is a worthwhile purchase for all those working in the field of neuromuscular disease.

CHARLES F. BOLTON

Acute Aneurysm Surgery, Pathophysiology and Management. By Keiji Sano, Takao Asano and Akira Tamura. 1987. Pp. 300. Vienna: Springer. Price DM 220.00.

In the first half of this 290 page book, Professor Asano has extensively reviewed the pathophysiological mechanisms complicating aneurysm rupture. He commences with acute ischaemic neurological deficits resulting from the immediate effects of the haemorrhage, and then progresses to delayed ischaemia, concentrating on the causes of the arteriopathic changes in the vessel wall. Finally he describes the mechanisms underlying ischaemic brain oedema. In all chapters, much emphasis is placed on the involvement of free radicals, hydroperoxides and eicosanoids. Although his own research interests are inevitably highlighted, these chapters provide an excellent review of the biochemical and pharmacological advances in this field.

The second half of the book begins with chapters by the other authors. In the first, Professor Tamura presents grading, angiography and CT findings and their relation to outcome in his own series of 272 patients. In the second, Professor Sano describes grading, timing of surgery and outcome in another series of 1047 patients. Unfortunately, when considering the timing of surgery, only 'surgical mortality' is reported rather than the more useful 'management mortality'. In addition, repetition occurs frequently; it would perhaps have been preferable if the authors had combined these studies and presented their results in a single chapter.

In the penultimate chapter, clinical studies leading from the extensive experimental work on 'vasospasm' and cerebral ischaemia are presented. Although few drugs have been adequately assessed in large double blind trials, the authors report favourable results from calcium antagonists, free radical scavengers, prostaglandin inhibitors and cerebral protective agents.

The last chapter describes operative techniques, but the line diagrams are no match for the variety of beautifully illustrated books currently available on this subject. Operative descriptions are brief and perhaps only of value to the most junior trainees. Rather than including the case report for each type of aneurysm, more experienced neurosurgeons may have benefited from a more detailed description of the subtle advantages and problems facing each approach.

Throughout the book the authors incorrectly use the term 'cerebral vasospasm' synonymously with 'cerebral ischaemia'; arterial constriction is unlikely to be the only factor involved in ischaemia. Spelling errors crop up frequently. A few authors are cited in the text and not included in the references. Numerous abbreviations are used and a separate list would be valuable, rather than frustratingly turning back over pages of text to find their meaning.

These shortcomings aside, I have no doubt that this book will sell well. It is compact and reasonably priced. It should prove popular with neurosurgeons and trainees alike, particularly those with an interest in the complex experimental field of cerebral ischaemia complicating aneurysm rupture.

K. W. LINDSAY

The Management of Persons with Spinal Cord Injury. By Mark N. Ozer. 1988. Pp. 120. New York: Demos. Price not stated.

In this paperback on the management of spinal cord injury, Mark Ozer seeks to develop new models of health care for persons with disability. The book follows the conventional pattern of a short introduction to the elementary anatomy and physiology of spinal cord injuries, with subsequent sections on the acute care, rehabilitation and continuing care of spinal injury patients.

The acute care section is written with a neurological approach and also from the approach of an American spinal injuries service. Patients are apparently not received immediately after injury, but clearly some weeks after they have undergone their acute care elsewhere, since under Dr Ozer's treatment plan he makes no mention of the major associated injuries. As 75% of patients, in the reviewer's experience, have major associated injuries, the prime concern of the treating physician must be to deal with those injuries while preserving neurological function, thus saving life. This book only considers the neurological manifestations. Dr Ozer goes into great detail about the indications for surgical fusion of the spine, which unbalances the whole section.

With regard to rehabilitation, there is a conventional discussion of bladder and bowel care. Dr Ozer then goes into considerable detail on the indications for upper limb tendon transfers to improve function. This is a specialized form of surgery which has only been undertaken in a small number of centres and demands the close cooperation between physicians, surgeons, physiotherapists and occupational therapists. It would be of interest to know whether he had had first-hand experience of these techniques and if so what was his assessment, as this is not apparent.

The book seems largely to be based on a review of the literature and I do not think the European reader who has experience of a different system of spinal care will find it valuable.

J. R. SILVER

Spinal Cord Dysfunction: Assessment. Edited by L. S. Illis. 1988. Pp. 303. Oxford University Press. Price £40.00.

The Spinal Trust has been set up to raise money to encourage basic research into spinal cord injury. Part of its activities was to set up a workshop to review latest developments in spinal injuries. This book is a workshop by specialists in neurology, neurophysiology, spinal injury and neuropathology to indicate the difficulties and possibilities of assessment and to emphasize the interdependence of clinical and experimental neurology.

The book is 300 pages long; as it is written by a multiauthor team it is not comprehensive and the chapters are uneven. Some authors have made a significant research contribution to the field and this is reflected in their chapters. The chapters are extremely varied. That by Fehlings and

Tator, who have a laboratory devoted to research into models as to how spinal injury can be produced, is excellent. The chapter by J. T. Hughes is too short and one would have welcomed further details on the dogmatic statements about the causation of syringomyelia by a valve-like mechanism with a pressure gradient into the syrinx. The long chapter on the radiology of spine and spinal cord injury by P. L. Cook is a superb exposition of the whole practical approach to the management of the radiology of spinal cord injury, by someone who is clearly closely conversant with the practical procedure, but some discussion of the vital x-rays of associated injuries would have been welcome.

There is a thoughtful chapter by Illis on the clinical evaluation of spinal cord injury in the chronic stage and a very worthwhile chapter by Woolf on the neuroplasticity of injury. That on neurological and neurophysiological evaluation by Wise, Young and Peter Mayer is not helpful. Alain Rossier's chapter is a superb review of the current state of therapy. It should be noted that of the authors mentioned so far, he is the only one currently treating spinal injuries. The chapter by Sedgwick is excellent on the modern neurophysiological techniques for evaluating spinal potentials. That by Cole is a good review of the whole subject, but the chapter by Massey suffers from the defect that he is clearly not working in the field of spinal injuries since he treats the bladder as though it were a neurophysiological preparation and only mentions infection in passing. Those of us that are actively concerned in the treatment of spinal injury are unfortunately having to see the ill-effects of infection, fibrosis and over-distension. Michael Swash's chapter on pelvic floor reflexes is an excellent account of the neurophysiological technique and that by Dimitrijevic is a stimulating review of this subject. Rothwell's chapter on cortical stimulation is again valuable. The book is difficult to read and each chapter repays careful study. Those who are seeking to learn how to treat spinal injuries will find that this book does not serve their purpose. It is for the advanced student of spinal injuries or spinal cord function and as such it is an invaluable source book.

J. R. SILVER

Current Topics in Pathology—Neuropathology. Edited by Colin L. Berry. 1988. Pp. 155. Berlin: Springer. Price DM 168.00.

Current Topics in Pathology is the title of a series of books published by Springer. Volume 76, *Neuropathology*, edited by Colin L. Berry is a small handbook for general pathologists covering four important aspects of neuropathology.

Professor J. H. Adams, of Glasgow, presents an excellent review on autopsy findings in traumatic head injuries, provides recommendations with regard to autopsy techniques and gives his views on the neuropathological findings in various forms of haemorrhage, hypoxic brain damage and brain swelling. The second chapter written by Dr Janice Anderson, of Cambridge, concentrates on viral diseases afflicting the nervous system. The most common forms of acute viral diseases are covered as well as some more rare, subacute and chronic conditions. Aspects on related diseases, such as postinfectious encephalomyelitis and slow viral infections, are also given. Professor R. O. Weller, of Southampton, is the author of the third chapter 'A General Approach to Neuropathological Problems'. This excellent contribution deals with general autopsy methods for investigation of the brain and spinal cord; classical histological techniques as well as many modern methods are reviewed. Nerve and muscle biopsies are also discussed. The last chapter, presented by Dr. C. L. Scholtz, of London, concerns brain changes in dementias. Basic cellular and subcellular alterations are discussed and special forms of dementing diseases are described in a very clear way.

There are 85 excellent figures and the volume is an important up-to-date handbook dealing with a selected group of important brain diseases. It can be strongly recommended as a handbook for general pathologists and it can equally well be recommended for those working in neuropathological laboratories as well as for anyone else interested in neuropathological changes in the human brain.

YNGVE OLSSON

Diagnostic Manual of Tumours of the Central Nervous System. By Anthony J. Franks. 1988. Pp. 146. Edinburgh: Churchill Livingstone. Price £45.00.

There is always a keen demand for a book that provides practical help in the interpretation of microscopical appearances and this is especially true of the subject of tumours involving the central nervous system. In recent years a number of volumes of varied merit have appeared, but there still seems to be a real need for a compact illustrated guide for those unfamiliar with the subject.

Dr Franks has designed his book 'to provide a practical bench manual for trainees . . .' and for 'experienced pathologists who occasionally have to deal with neuropathological material'. The needs of neurosurgeons and radiotherapists are also considered. Within the compass of 146 pages he has achieved an informative text subdivided into 14 chapters, each with a select reference list for further reading. There are 271 illustrations and a useful index.

The chief problems in a small handbook are to know what information may resonably be left out and how to help the reader to understand the images that are displayed. The pictures include smear preparations, cryostat sections, a few electron micrographs, a little CSF cytology (cytospin) and occasional immunohistochemical preparations in addition to the paraffin wax-embedded sections stained with haematoxylin and eosin that form the core of the book. No glial tumours are shown stained with phosphotungstic acid-haematoxylin, and there are no toluidine blue preparations of smears. A very much larger volume would be necessary to show the same tumour in smear, cryostat, CSF cytology and definitive histological preparations and to try to explain the underlying reasons for the variation in appearances with different methods. As it stands, the novice may find the effect confusing, while the more advanced student of neuropathology requires greater details for the book to be of real value. The pictures are of varied quality, those of the pineocytoma, for instance, cannot be said to facilitate recognition of this lesion. The classification used is chiefly based upon that of the Armed Forces Institute of Pathology Fascicle (1972), with the addition of the controversial term 'primitive neuroectodermal tumour' used as a synonym for medulloblastoma, pineoblastoma and neuroblastoma. The inherent problems of interpreting biopsies of childhood intracranial tumours are not resolved by the uncritical use of this inclusive term and perhaps deserve a more lengthy examination than can be included in this volume.

R. O. BARNARD

Epinephrine in the Central Nervous System. Edited by Jon M. Stolk, David C. U'Prichard and Kjell Fuxe. 1988. Pp. 379. Oxford University Press. Price £75.00.

Epinephrine (adrenaline) has become fashionable again. A resurgence of interest started in 1974 when Saavedra discovered the presence of PNMT, the enzyme which converts noradrenaline to adrenaline, in the brain, and more recently new technological advances have allowed studies of adrenergic cell groups in various brain areas. It is these recent changes which are addressed by this volume which is a compilation of papers presented at the Maryland Psychiatric Centre—at an undisclosed date. The most recent references in most chapters were 1985 with a few chapters quoting an occasional 1986 paper.

The strengths and weaknesses of the book reflect the usual problems of published proceedings on a disparate subject. Thus the coverage is broad, and in spite of the title includes not only the brain but also platelets, adrenal medulla and vascular receptors, etc. There are excellent chapters on morphology of PNMT neurons from the Swedish and Italian groups of Hökfelt, Fuxe and Agnati, as well as mapping of receptors by Unnerstall and Kuhar and ultrastructural studies by Kalia and colleagues. Following this very good start, the book begins to lose its sense of purpose and any logical sequence, with chapters which have considerable repetition, overlap and little evidence of cross-referencing. There are 34 chapters and although most are of interest in themselves they do not provide a clear overview of central nervous system adrenaline—rather a series of reviews of individual study areas. These do, however, include interesting papers on the control of PNMT, regulation of anterior pituitary hormones, receptor subtypes and postreceptor second messenger coupling. These are followed by further chapters on electrophysiological and cardiovascular aspects of centrally administered adrenaline.

The print itself is not very pleasant to read and the figures not only have no standard format but are extremely variable in quality. At £75 this seems remiss of the publishers.

Overall, this is a timely book which will be of interest to many neurochemists. It is, however, not an easy book to read and is not detailed enough to be a full reference volume.

STAFFORD LIGHTMAN

Research on Multiple Sclerosis. Third edition. By Byron H. Waksman, Stephen C. Reingold and William E. Reynolds. 1987. Pp. 107. New York: Demos. No price stated.

This small paperback book is designed to explain to the lay person, particularly the MS patient and her or his relatives, why it is worth the American National Multiple Sclerosis Society spending $7 million annually on research. The emphasis is on laboratory research; clinical and nuclear magnetic resonance studies and treatment trials receive scant mention. The flavour is technical and humourless but the scientifically minded lay person should be able to follow the gist of the arguments and could not fail to be impressed by the volume and variety of work. For the specialist it is tantalizing to read of new information without having the references to check the strength of the evidence. One is left with two impressions (1) that the answer is just around the corner but the building is a polygon and the corner is not labelled and (2) that if Stephen Hawking can make astronomy and quantum mechanics amusing and almost comprehensible, someone should be able to do the same for MS research. This book is unlikely to sell well at airports.

R. A. C. HUGHES

Control of Head Movement. Edited by Barry W. Peterson and Frances J. Richmond, 1988. Pp. 332. Oxford University Press. Price £35.00.

This book results from a satellite symposium of the XXX Congress of the International Union of Physiological Sciences in the summer of 1986. It is not simply a collection of heterogeneous symposium proceedings but a comprehensive review of a field of growing interest among life scientists with differing backgrounds. After decades of oculomotor research which was characterized by the restricted and therefore often unnatural experimental approach of either eye movements relative to a stationary head or the vestibulo-ocular reflex in yaw, two more complex research topics have arisen which fascinate this well established research group: (1) three dimensional control of eye-movements according to the different planes of the semicircular canals; (2) eye-head coordination.

The twenty chapters bring together international authorities on the physiological mechanisms responsible for head movement. They begin with a description of the multisegmental articulation and the many pairs of muscles that link the skull, spinal column and the shoulder girdle in mammals and man which make biomechanical modelling of head movement so difficult. Two contributions deal with the peripheral organization of cervical motoneurons as well as receptors of the neck muscles and joints. Most of the remaining chapters concentrate on individual research activities on afferent and efferent projections, the tectoreticulospinal system, vestibular, spinal and supraspinal control of neck reflexes, eye-head coordination and visual orientation. The models of voluntary head movement presented by Stark *et al.* provide a first approach to the neurological patient, whereas the final chapter on clinical disorders of head movement reveals the considerable gap between basic research and clinical application.

This is a good book which provides valuable information for neuroscientists on the physiology of head movements; however, it has less to offer for clinically orientated neurologists.

THOMAS BRANDT

The Human Brain. By Paul Glees. 1988. Pp. 204. Cambridge: Cambridge University Press. Price £32.50.

This book is based on, and extensively derived from, the author's earlier work, *Das menschliche Gehirn* of 1971. As in the great majority of standard neuroanatomy texts, the chapters fall into two principal classes: those dealing with general aspects of the nervous system, such as its microscopic structure and blood supply, the nerve impulse, and evolution; and those concerned with specific parts or systems, such as the cerebral hemispheres, the spinal cord and the visual pathways. However, in many chapters the balance of material does not follow that generally found in standard undergraduate textbooks. While the emphasis is strongly on morphology, certain aspects, usually concerning function or comparative anatomy, tend to be emphasized relatively more than is customary. Nevertheless, the various aspects are well integrated with one another. There is also a tendency to approach topics from the standpoint of a review or a commentary. In some instances this requires a degree of familiarity by the reader with basic factual details not readily available in this book. Large numbers of references to the research literature are cited, most of which precede the publication of the German version in 1971. References to clinical material are relatively limited.

This book provides an individual perspective on neuroanatomy, and will be found most useful by the undergraduate in rounding off the basic factual information available in more concise texts. It is lavishly illustrated, mainly with clear line drawings of good quality, many of which are taken from the author's earlier work cited above. The quality of photographic reproduction, mainly of light and electron micrographs, is generally satisfactory. It is clearly written, but contains rather a large number of typographical and printer's errors.

JOHN P. FRAHER

Handbook of Clinical Psychoneuroendocrinology. Edited by C. B. Nemeroft and P. T. Loosen. 1987. Pp. 502. Chichester: Wiley. Price £8.50.

This is a valuable reference handbook of clinical psychoneuroendocrinology. The large and rapidly growing subject is reviewed in 24 chapters. Between them they cover most of the principal findings in the field, together with about 5000 key references.

The book is written for the clinician and provides what is probably the most comprehensive account that is available of the hormonal changes that are seen in the various psychiatric disorders. It also includes some coverage of the even more important topic of the psychiatric effects of endocrine disorders. While its comprehensive coverage is the main strength of this book its principal weakness concerns its lack of critical perspective in certain sections. An uninformed reader could from this book draw the erroneous conclusion that psychiatric diagnosis can be assisted by the appropriate use of neuroendocrine tests.

For the hardened cynic the book will be a useful reference book. More critically balanced accounts of the subject are available.

S. CHECKLEY

Textbook of Neuropsychiatry. By Michael D. Franzen and Mark R. Lovell. 1988. Pp. 219. Cambridge University Press/American Psychiatric Press. Price £15.00.

This book, as pointed out in the Introduction, has been compiled to highlight cardinal issues and key points raised in each chapter of the 490 page *American Psychiatric Press Textbook of*

Neuropsychiatry. Thus, the study guide is divided into four sections, covering such topics as Evaluation and Basic Principles (the neuropsychiatric evaluation, brain imaging, laboratory testing, neuropsychological assessment, neurotransmitters and neuroreceptors), Organic Mental Disorders (delirium, dementia, alcohol-induced disorders, substance-induced disorders), Treatment Issues (psychosocial, psychopharmacological, cognitive, rehabilitation and legal aspects) and Specific Neuropsychiatric Disorders. This latter section is devoted to neuropsychiatric aspects of traumatic brain injury, cerebrovascular disease, epilepsy, headache, facial pain, sleep disorders, degenerative, metabolic and endocrine disorders, vitamin deficiency states, cerebral infections and tumours, and the neuropsychiatric disorders of childhood and adolescence.

The study guide takes the form of a multiple choice question (MCQ) assessment of knowledge as derived from the Textbook. The MCQs have several formats, such as (1) selecting 1 of 5 responses to a statement or question which is the best choice/most complete answer, or (2) selecting A if 1, 2, and 3 are correct, B if 1, 3 are correct, C if 2, 4 are correct, D if only 4 is correct and E if all are correct.

The book thus offers practise in a variety of methods encountered in the MCQ examination settings. Furthermore, unlike some MCQ books which do not offer this facility, the guide gives the correct answer followed by a brief discussion of the arguments for and against each of the possible answers, thus offering a summary of the salient points relevant to the specific topics covered, and including, in some cases, specific cited references. The MCQs assess a wide variety of knowledge such as definitions of terms, historical and epidemiological data, clinical and laboratory information, as well as relevant research and theoretical issues.

In its favour, it is small, paperback and easy to carry, in addition to being reasonably priced, and therefore offers a valuable adjunct for an individual who may either own the Textbook, especially when preparing for examinations involving MCQs. As intended, the topics of the guide parallel exactly those of the Textbook; however, the MCQs can be answered by individuals having knowledge in neuropsychiatry in general (or examination candidates studying other neuropsychiatric or organic psychiatry textbooks, for example, Lishman, Roberts, Trimble).

A deficiency in the book, but one must acknowledge that it is not within the designated brief of the book, is that several neuropsychiatric topics such as the psychiatric aspects of Parkinson's disease, multiple sclerosis, movement disorders, and other neuropsychiatric aspects of epilepsy (aggression, sexual dysfunction, affective disorders) are not covered.

In summary, providing an individual benefits from the MCQ type approach to learning or teaching, and bearing in mind that the guide does not purport to cover the whole subject of neuropsychiatry, it is a good, concise and affordable book, which is recommended for both personal and medical libraries.

MARY ROBERTSON

ANNOUNCEMENTS

International Symposium on Pediatric Neuro-Oncology

This symposium, sponsored by the Children's Hospital and Medical Center, Seattle, the Children's Hospital of Philadelphia and the University of Washington School of Medicine, will be held in Seattle, Washington, on June 1-3, 1989. For further information, contact CME, SD-50, University of Washington, Seattle, Washington 98195, USA.

Sixteenth International Summer School of Brain Research

This will be held in Amsterdam, The Netherlands, on August 28-September 1, 1989. The topic will be 'Function, Plasticity and Pathology of the Prefrontal Cortical Systems in Human and Animal Nervous Systems'. For further information, contact Ms Tini Eikelboom or Dr H. B. M. Uylings, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam 20, The Netherlands.

Medical Ultrasound Residential Courses/Workshops

Introductory residential course/workshops on 'Non-invasive Vascular Diagnostic Techniques' will be held in Southampton on May 15-17 and October 18-20, 1989 with particular emphasis on continuous and pulse wave Doppler ultrasound. Intensive three-day course/workshops on 'Blood Vessel Imaging using Ultrasound Techniques', covering both the basic principles of these imaging techniques and the latest developments in the assessment of arterial disease will be held on May 17-19 and October 16-18, 1989. Full details and registration forms may be obtained from K. N. Humphries, Medical Ultrasound Courses, 10 Swale Drive, Woodland Park, Chandler's Ford, Hampshire, UK.

The Volvo Award for CNS Injury Research 1989

In order to encourage research aimed at injury prevention analysis and mitigation of central nervous system injuries, the Volvo Company of Göteborg, Sweden, has sponsored an award for 1989 of US$ 5.000. Papers entering the contest must contain original material, not previously submitted for publication. Multiple authorship is acceptable. The manuscripts, in English, should be full length, including original illustrations, in a form suitable for submission as an original paper (not postgraduate thesis) to a scientific journal. One original and 5 copies of each paper in full must reach the address below *not later than June 1, 1989*. One of the authors should be prepared to come to New Delhi, India, at his own expense, for the 9th Congress on Neurological Surgery, October 8-13, 1989 to present the paper and to receive the award.

The board of referees will be chaired by Professor D. Stålhammar and will contain members chosen by the Committee of Neurotraumatology of the World Federation of Neurosurgical Societies. Further information may be obtained from Professor Stålhammar, Department of Neurosurgery, Sahlgren Hospital, S-413 45 Göteborg, Sweden.

Erratum

Aging and the Brain. Volume 32 of the series on Aging. Edited by Robert D. Terry. 1987. Pp. 328. New York: Raven Press. Price $91.00.

We regret that in the review of this book (*Brain*, 111, p. 1555) the price was quoted as $180.00 instead of $80.00. However, the publishers have written informing us that the international price for this book is now $91.00, reflecting the 1989 retail price increase.

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Travel grants for young neuroscientists

The Guarantors of *Brain* are prepared to consider applications for contributions towards travel costs from neuroscientists under the age of 40 working in the United Kingdom.

1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:

   (a) an abbreviated curriculum vitae and a list of any relevant publications; (b) statement of age and post currently held; (c) a concise account of the purpose of the proposed visit; (d) a recommendation from the head of department (where appropriate); (e) a letter of acceptance from the department to be visited; (f) a statement of costs likely to be incurred, and of other applications for funds that have been made. Advantage should always be taken of reduced air fares when available.
2. Applications will also be considered for contributions to the cost of attending specialized symposia of particular importance to the applicant's research. Documents as in (a), (b), (c), (d) and (f) above should be submitted at least three months before the date of the meeting, accompanied by a statement of what other applications for financial aid have been made and of any contributions by the symposium organization.
3. Only exceptionally will applications for assistance to attend larger international congresses be entertained. Successful applicants will be expected to submit a brief report on the conclusion of their visit.

Four copies of all documents should be submitted to: Professor D. A. S. Compston, Department of Neurology, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.

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THE ROLE OF CEREBELLAR STRUCTURES IN THE EXECUTION OF SERIAL MOVEMENTS

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SUMMARY

Thirteen patients with bilateral cerebellar disease and 12 patients with unilateral cerebellar disease were instructed to execute movement sequences in response to a simple reaction signal. Each to-be-executed sequence consisted either of a single, two, or three keypress components. Evidence for cerebellar involvement in the execution of programmed responses was sought in the pattern of response onset times and interkeypress times. Patients with mild bilateral cerebellar dysfunction or mild unilateral dysfunction, and neurologically unimpaired subjects showed increases in response onset time as sequence length increased from $L = 1$ to $L = 3$. In contrast to this, there were negligible or no effects of sequence length on response onset time in patients with moderate bilateral cerebellar dysfunction and in patients with moderate unilateral cerebellar dysfunction who responded with the hand ipsilateral to the lesion. Furthermore, cerebellar dysfunction was associated with significantly slower interkeypress reaction times. These results support the hypothesis that the translation of a programmed sequence of responses into action involves cerebellar structures which schedule a sequence of ordered responses before onset of movement.

INTRODUCTION

Acute damage or chronic atrophy of the cerebellum affects primarily complex motor action. Although cerebellar damage does affect simple movements, it is the execution of the more complex sequential movements which appears most vulnerable. The cardinal clinical sign of cerebellar damage is a 'decomposition of movement' (Holmes, 1917, 1939) in which serial muscle synergies of complex movements are decomposed into independent sequential constituents which are executed with errors or force, amplitude, and timing.

Decomposition of movement could occur during functionally distinct phases of action. It could occur during the *planning* (or conception) of movements, involve

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the *execution* of a complex response, or some intermediate phase. Noting that cerebellar dysfunction does not abolish complex movements and that cerebellar stimulation does not evoke a large number of complex responses, Brooks (e.g., 1984*a*, *b*) suggested that 'cerebellar contributions appear to lie in the less complex packaging of planned motor acts'. This view implies that the cerebellum is not critical for the generation of abstract motor plans; instead, it appears to control the parametric translation of a motor plan into action.

Some complex actions, which are composed of a number of constituent responses, can be executed at a rate too fast to be guided by sensory feedback. A neural representation of the entire action appears to be available before response onset which, when activated, triggers the automatic execution of the complex action as a single, fluid unit (Marsden, 1982). Since the hallmark of cerebellar damage is a decomposition of complex actions and an inability to execute movement sequences smoothly and swiftly, cerebellar damage could interfere either with the generation of a neural (motor plan) representation which comprises all components of a complex action, or with the parametric translation of a motor plan into action.

The current investigation tested the hypothesis that cerebellar damage disables the execution of a planned sequence of responses. An experimental paradigm developed by Sternberg *et al.* (1978) was used to measure simple reaction time (RT) to initiate movement *sequences* of varying complexity. Sternberg *et al.* found that the RT to initiate the first movement component of a sequence of responses (either spoken or typewritten) increased linearly with the length of the to-be-executed sequence. To account for the effect, it was proposed that an abstract representation of a response sequence (a motor program) is assembled before the initiation of the motor sequence and loaded into a 'motor buffer'. This programming phase is followed by the *execution phase* which is initiated when the reaction signal is perceived. During the execution phase, the motor program must be read out from the buffer to specify the spatiotemporal sequence of activation of peripheral muscles. As the number of component responses increases, so does the time required to read the motor buffer and to group the responses in their proper sequence, resulting in an increase in latency to initiate the first response component in the sequence (in the following this will be referred to as the 'sequence length effect'). Within this framework, the sequence length effect reflects real-time constraints on the translation of a programmed sequence of responses into action. The sequence length effect can be used to study this process in a way which is independent of slowness of peripheral responses, tremor, or other peripheral factors which can also affect RTs of cerebellar patients.

PATIENTS AND METHODS

In the present experiments, patients with bilateral lesions (Experiment 1) and unilateral lesion (Experiment 2) to the cerebellum executed a sequence of keypress responses consisting of either a single, two, or three response components. If a cerebellar lesion impairs the translation of a programmed sequence of responses into action, then patients should execute a programmed movement sequence as if it consisted of independent response constituents and the sequence length effect in the T1 RTs should be reduced or absent. If, instead, cerebellar dysfunction does not affect the translation of a programmed sequence of responses into action but slows the rate of the translation process, then an abnormally large sequence length effect should be obtained. A comparison of T1 RTs with interkeypress RTs for noninitial responses can provide additional data to test the hypotheses. If cerebellar dysfunction disabled the translation of a programmed sequence of responses into peripheral response parameters prior to response onset, then noninitial responses should be executed as independent response units with relatively long interkeypress RTs. Consequently, a lack of a sequence length effect in the T1 data should be associated with long interkeypress RTs. If, however, cerebellar dysfunction simply slows the translation of a programmed sequence of responses into peripheral response parameters, then a cerebellar lesion should not affect interresponse times and noninitial responses should be executed with relatively short interkeypress RTs. Consequently, an abnormally large sequence length effect in the T1 data should be associated with relatively short interkeypress RTs. In the following, we will use the term 'negative position effect' when interresponse times are longer than T1 RTs and 'positive position effect' when interresponse times are shorter than T1 RTs.

Response onset times and interresponse times may measure somewhat different processes. The reaction signal has to be encoded before-response onset but no comparable visual coding needs to be done for noninitial responses. Furthermore, it appears that the translation of a motor program into action parameters occurs before response onset so that it affects T1 RTs but not interkeypress RTs. Nevertheless the comparison of T1 RTs (which include different types of start-up time) with interkeypress RTs (which do not include these start-up times) may be informative in that it may assess benefits associated with the execution of preplanned noninitial responses.

EXPERIMENT 1

Methods

Subjects. Thirteen patients with bilateral cerebellar dysfunction were tested. All patients suffered from chronic cerebellar disease and were outpatients of the Neurology Clinic at the University of Tübingen, West Germany. There were 8 men and 5 women, ranging in age from 20–74 yrs (mean 46 yrs). Two patients had Friedreich's ataxia and 4 had olivopontocerebellar atrophy (OPCA) with mainly cerebellar signs and minimal involvement of basal ganglia, pons, and spinal cord as revealed by clinical examination, CT scan, electro-oculography, evoked potentials (brainstem acoustic and sensory evoked potentials) and posturography. Six patients had diffuse cerebellar atrophy of unknown origin without clinical deficits outside the cerebellum. Patients with multiple sclerosis, chronic alcoholism, drug abuse, toxic cerebellar atrophy, or pathological CSF were excluded. A summary of these diagnoses, together with a scaling of the clinical signs of upper limb function is provided in Table 1. The scaling was performed by a neurologist who did not participate in the present study. A score of 0 indicates relatively normal function, a score of 5 severe dysfunction. Dysdiadochokinesia was evaluated by asking the patient to supinate and pronate the outstretched hand as fast as possible. Dysmetria was tested by asking the patient to point with the index finger to his/her nose and to follow and touch as fast as possible the suddenly moving finger of the examiner. Intention tremor was investigated with the same procedure but also during reaching for a target in front of the patient.

Eight neurologically unimpaired adults, tested by Rafal *et al.* (1987) in an identical task under comparable testing conditions were used as control subjects. These included 2 men and 6 women ranging in age from 45–78 yrs.

Apparatus and procedure. Reaction signals to begin movement execution were shown on a cathode ray tube (CRT) which was placed on top of a table approximately 60 cm in front of the patient's

TABLE 1. CLINICAL DATA FOR PATIENTS PARTICIPATING IN EXPERIMENT 1

					Dysdia		*FNT**		*Int. tremor**	
Patient	*Age (yrs)*	*Sex*	*Duration (yrs)*	*Diagnosis*	*RH*	*LH*	*RH*	*LH*	*RH*	*LH*
Mild dysfunction										
A.D.	35	M	2	UO	1	1	1	1	0	0
H.O.	53	F	5	UO	2	2	1	1	1	1
R.A.	20	M	6	UO	2	2	2	3	0	0
R.O.	60	F	2	UO	2	2	1	1	0	0
B.U.	53	M	3	OPCA	3	3	1	1	2	2
H.E.	56	M	3	OPCA	2	2	2	2	1	1
M.A.	48	F	20	OPCA	3	3	2	2	1	1
Moderate dysfunction										
K.N.	51	M	10	UO	3	3	3	3	2	2
R.E.	74	F	9	UO	4	4	4	4	4	4
S.C.	60	M	5	UO	2	2	3	3	2	2
H.A.	24	F	10	Fried.	2	2	2	2	3	3
S.T.	25	M	12	Fried.	3	3	4	4	2	2
J.Z.	36	M	15	OPCA	3	3	3	3	3	3

* Disability ratings: 0 = minimal dysfunction, 5 = severe dysfunction. RH = right hand ratings; LH = left hand ratings. Dysdia = dysdiadochokinesia; FNT = finger-to-nose test, Int. tremor = intention tremor; OPCA = olivopontocerebellar atrophy; Fried. = Friedreich's ataxia; UO = lesion of unknown origin.

eyes. A response board with 4 spatially adjacent keys in its centre was placed in front of the CRT. Each patient sat in front of the table, rested his/her elbow on the table surface, and placed the 4 fingers of either the right or left hand on the 4 keys of the response board. Each key was 2.1 cm wide and 5 cm long which permitted a comfortable positioning of the fingers. Pressing a key with a finger resulted in a vertical displacement of 2 mm and triggered a microswitch which was mounted below each key. Each microswitch was connected to a microcomputer which controlled the experiment and measured reaction times to the nearest millisecond.

Patients were tested individually. At the beginning of the experiment, each patient was familiarized with the equipment and instructed which sequences of manual responses were to be executed. Three different blocks of sequences were used, each of which contained either a single keystroke with the index [I] finger (L = 1), a sequence of two keystrokes with the index finger as first and the ring finger as second response component [I-R] (L = 2), or a sequence of three keystrokes (L = 3) with the index finger as first, the ring finger as second, and the middle finger as third response component [I-R-M]. Each hand was tested separately. Sequence length was blocked so that the response to be made was the same for every trial in a block. Thus subjects had information of the movement to be made which allowed them to prepare the sequence fully before the reaction signal appeared. Subjects were instructed to execute the sequences as 'quickly and accurately' as possible and try to execute the sequences smoothly 'like a single movement'. Because our goal was to study the programming and execution of learned movement sequences, subjects practised each of the response sequences until they reported that they could no longer improve (approximately 30 practice trials per condition). After this, experimental trials were initiated.

Each trial began with the display of the outlines of a bright square with a side length of 10 cm in the centre of the screen. Half a second later, a 50 ms tone was sounded to alert the patient; 250 ms after the tone, the reaction signal, consisting of a large bright 'X' sign was shown in the centre of the square. Patients were instructed to tap the prespecified sequence of responses (L = 1, L = 2, or

$L = 3$) as swiftly as possible after the occurrence of the reaction signal. After the required number of component responses were executed, the screen went blank for 3 s after which the central square was lit and another trial began. Feedback was given after each trial. A high pitched tone for a correct response, a low pitched tone if the sequence was incorrect or if, for any reason, the correct response was not executed within 3000 ms of the reaction signal. No catch trials were included and the regular and predictable sequence of each trial was designed to encourage motor programming. To minimize the degree to which premature responses could affect the outcome, subjects were carefully monitored for responses which occurred before the reaction signal appeared; when these occurred, subjects were cautioned not to initiate the action before the reaction signal occurred. Moreover, RTs of less than 150 ms were excluded from analysis. Each patient was tested on 12 blocks of 30 trials each. Sequence length $L = 1$ to $L = 3$ was tested in separate blocks of trials so that each hand was used in 2 blocks of trials of a particular sequence length. The order of the blocks of trials of a given sequence length was randomized. Seven randomly selected subjects started a doublette of blocks of a particular sequence length with the right hand and then switched to the left hand, the reversed order of hands was used for the remaining patients. The computer kept a record of the intervals between the onset of the reaction signal and the sequence initial keypress responses (T1), between the onset of the initial and the second keypress responses (T2), and between the onset of the second and third keypress responses (T3).

RESULTS AND DISCUSSION

Responses were considered correct when they were initiated within 3 s following the onset of the reaction signal and when component responses were executed in their correct order. Responses with reaction times for the initial response (T1) of less than 150 ms were excluded from analysis because these extremely short responses were assumed to be due to anticipations. Approximately 11% of the trials were classified as errors. An inspection of errors suggested that they were primarily caused by unintended keypress responses; no other systematic error pattern was evident. RTs of correctly executed trials were subjected to statistical analyses. Following the earlier study (Rafal *et al.*, 1987), response onset T1 latencies for initial index finger movements were analysed as a function of sequence length to determine sequence length effects; furthermore, T1 latencies were compared with interkeypress latencies for noninitial responses (T2 and T3) to determine position effects.

Median T1 RTs of bilateral cerebellar patients are shown in fig. 1, which also shows the corresponding T1 data of 8 neurologically unimpaired subjects who were tested in an earlier study (Rafal *et al.*, 1987). The data were subjected to an analysis of variance (ANOVA) with the between subjects factor groups (cerebellar damage vs control) and the within subjects factor sequence length ($L = 1$, $L = 2$, and $L = 3$). T1 RTs of control subjects were somewhat shorter than T1 RTs of cerebellar patients; this difference was not significant $F < 1$. Overall, T1 increased with sequence length, $F(2,38) = 17.33$, $P < 0.001$. More importantly, this main effect of sequence length was qualified by a significant interaction of sequence length and groups, $F(2,38) = 3.93$, $P < 0.05$. As shown in fig. 1, for control subjects, response onset time to execute the identical index finger movement increased by 93 ms as sequence length increased from $L = 1$ to $L = 2$ and increased by an additional 72 ms as sequence length increased from L = 2 to L = 3. The corresponding increases of bilateral cerebellar patients were significantly smaller and amounted to 35 ms and 26 ms, respectively. These results agree with the hypothesis that cerebellar disease impairs the translation of a programmed sequence of responses into action.

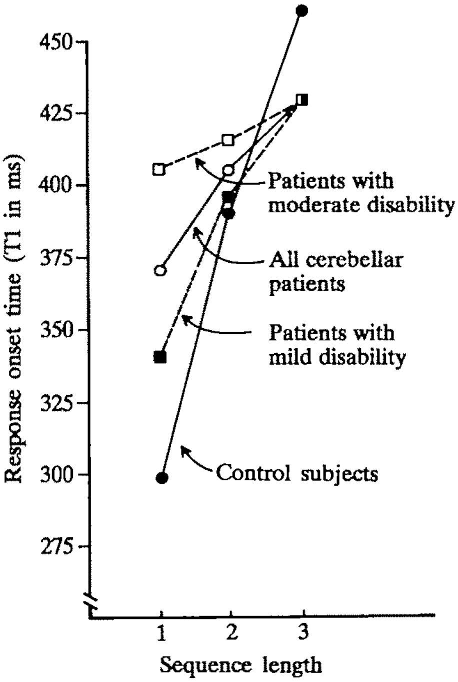

FIG. 1. Sequence length effect in Experiment 1. Reaction time to initiate the first response (T1) in the sequence as a function of sequence length: L = 1 for index finger responses, L = 2 for index and ring finger response sequences, and L = 3 for index, ring, middle finger response sequences. All cerebellar patients (solid line, open circles) are compared with normal control subjects (solid line, closed circles). In addition, a subgroup of patients with moderate disability (dashed line, open squares) is compared with a subgroup of patients with mild disability (dashed line, closed squares).

Additional support for this hypothesis was obtained in a separate post hoc analysis. An inspection of the individual patient data revealed a sequence length effect for some patients but not for other patients. Furthermore, the inspection suggested a correlation between the severity of cerebellar disability and the magnitude of the sequence length effect. Such a correlation could be theoretically important in that it would provide additional evidence for cerebellar involvement in the translation of a programmed sequence of responses into action. To test this, we separated the patient data into two approximately equal-size groups: one group of 7 patients with mild clinical disability and another group of 6 patients with moderate clinical disability. The grouping was based on disability ratings for upper limb function (dysdiadochokinesia, finger-to-nose test, and intention tremor). Patients with an average disability rating of less than 2.3 (*see* Table 1) were classified as mildly disabled, and those with a rating of more than 2.3 as moderately disabled. This procedure separated patients into 2 groups: a mildly impaired group with patients without or with only minimal disability in using their hands for daily activities and a moderately impaired group with some disability. Patients with severe signs could not perform the task and were therefore not represented in the study. An ANOVA with the factors severity of disability (mild vs moderate) and sequence length was applied to this new set of T1 data. There was no main effect of disability, F < 1, and T1 RTs increased with sequence length, F(2,22) = 14.59, $P < 0.001$. More critically, the analysis showed that the sequence length effect was larger for mildly disabled patients than for moderately disabled patients (*see* fig. 1). This interaction was significant, F(2,22) = 5.25, $P < 0.025$, providing further support for the hypothesis that cerebellar structures control the translation of motor programs into action, presumably by specifying the spatiotemporal parameters of the complete sequence of responses prior to response onset.

To assess *position effects*, RTs for the sequence initial response (T1) were compared with interkeypress RTs (T2 and T3). T1 and T2 RTs for 2 component movements of L = 2 sequences were 407 ms and 360 ms for patients, and 392 ms and 352 ms for control subjects. The corresponding T1, T2, and T3 RTs for 3 component movements of L = 3 sequences were 430 ms, 373 ms, and 415 ms, respectively, when patients were tested, and 463 ms, 392 ms, and 369 ms when control subjects were tested. One ANOVA was applied to the 2 component sequence index/ring finger and another ANOVA was applied to the 3 component sequence index/ring/middle finger. Each of the two analyses contained one between subjects factor (patients vs controls) and one within subjects factor (response position: first, second, (third)). Both ANOVAs failed to reveal significant main effects or significant interactions even though there was an expected tendency towards larger position effects in control subjects.

An inspection of individual patient data was, again, informative. It showed positive position effects for patients with mild cerebellar disability and negative position effects for patients with moderate cerebellar disability. To evaluate this tendency, separate post hoc ANOVAs with the factors severity of disability and response position were applied to L = 2 and L = 3 sequences. The results, as shown in fig. 2, revealed a large positive position effect in patients with mild disability and a negative position effect, with shorter response onset RTs than interkeypress RTs, in patients with moderate disability. This interaction approached statistical significance in L = 2 sequences, F(1,11) = 3.42, $P < 0.09$, and was significant in L = 3 sequences, F(2,22) = 5.87, $P < 0.01$.

To summarize, the results of Experiment 1 revealed two major findings. Cerebellar patients showed a smaller sequence length effect and a tendency towards smaller position effects than control subjects. Additional post hoc analyses revealed that the magnitude of sequence length and position effects was qualified by patients' disability. Mild clinical disability was associated with relatively normal sequence length and position effects; moderate clinical disability, in contrast, virtually eliminated position and sequence length effects.

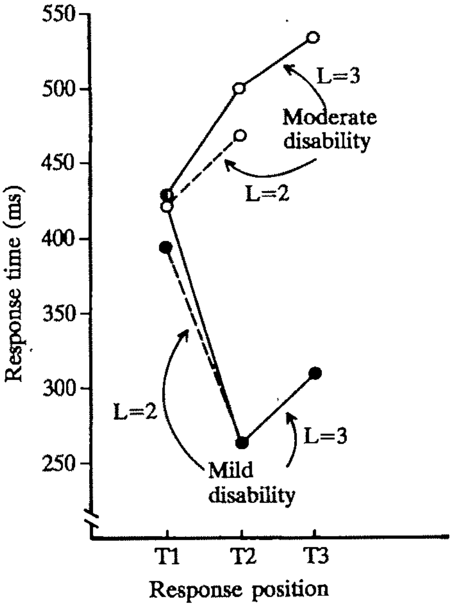

FIG. 2. Position effect in Experiment 1. Response times as a function of the position of response components in the sequence are shown for patient groups with moderate and mild disability. L = 2 sequences comprise the interval between the reaction signal and the first keypress response (T1) and the interval between the first and second keypress response (T2). L = 3 sequences comprise the interval between the reaction signal and the first keypress response (T1), the interval between the first and second keypress response (T2), and the interval between second and third keypress response (T3). Moderate impairment is indicated by open circles, mild impairment is indicated by closed circles. Data from L = 2 sequences are shown in dashed lines, data from L = 3 sequences are shown in solid lines.

These findings indicate that cerebellar structures are implicated in the translation of a programmed sequence of responses into action. Elements of a practised sequence of ordered movements, which are grouped into response ensembles prior to movement onset in control subjects and in patients with mild cerebellar disability, were executed as functionally independent units in patients with moderate cerebellar disability.

EXPERIMENT 2

The results of Experiment 1 revealed a relationship between bilateral cerebellar disease and the magnitude of sequence and position effects. However, since cerebellar disease was a between-subjects factor, alternative interpretations are possible. For example, patients with moderate disability may have been less alert than patients with mild disability or control subjects. A deficit in alerting, rather than a deficit in motor planning, might thus account for some of the results. It is also possible that patients with moderate disability suffered from larger memory deficits than other subjects which may have interfered with their execution of noninitial responses. A further possibility is that patients with moderate disability were more likely to suffer from extracerebellar damage. Consequently, extracerebellar damage, rather than damage to the cerebellum itself, could account for the results of Experiment 1.

Experiment 2 controlled these possibilities. Twelve patients with unilateral damage to the cerebellum were tested in identical conditions to Experiment 1. In all 12 patients, one hand was unimpaired and one hand was mildly to moderately impaired due to cerebellar damage. Experiment 2 was designed so that each patient served as his/her own control by comparing the intact (contralateral) hand with the impaired (ipsilateral) hand. If the findings of Experiment 1 were specific to cerebellar damage, then a larger sequence length effect should be obtained for patients' contralateral responses than for their ipsilateral responses; furthermore, interkeypress RTs should be shorter for contralateral responses than for ipsilateral responses. In contrast, no systematic differences between hands should emerge in these patients if general performance factors, e.g., attention, alerting, memory, or global CNS damage, underlie sequence and position effects.

Methods

Subjects. Twelve patients (5 male, 7 female) with unilateral cerebellar lesion confirmed by CT scan were tested. They were aged between 20 and 69 yrs (mean 43 yrs). Seven chronic patients were tested at the Neurology Clinic at the University of Tübingen; these patients were subjected to the same clinical examinations as the 13 bilateral patients who participated in Experiment 1. One acute patient was tested at Roger Williams Hospital in Providence, Rhode Island, and 4 chronic patients at the Good Samaritan Hospital and Medical Center, Portland, Oregon. A descriptive summary of the 12 participating patients is given in Table 2.

Apparatus and procedure. The identical apparatus and procedure were used as in Experiment 1.

TABLE 2. CLINICAL DATA FOR PATIENTS PARTICIPATING IN EXPERIMENT 2

Patient	*Age (yrs)*	*Sex*	*Duration (yrs)*	*Diagnosis*	*Dysdia*		*FNT**		*Int. tremor**	
					RH	*LH*	*RH*	*LH*	*RH*	*LH*
Mild dysfunction										
A.C.	50	F	14	Vasc., L	0	2	0	1	0	0
O.E.	53	F	2 mo.	Vasc., L	0	1	0	1	0	0
B.O.	49	M	5	Vasc., R	1	0	1	0	0	0
R.U.	20	M	5	Tumour, R	1	0	1	0	0	0
P.R.	47	F	5	Vasc., R	2	0	2	0	1	0
K.A.	69	M	1	Tumour, L	1	1	0	2	0	2
Moderate dysfunction										
B.R.	45	F	4	Vasc., L	0	2	0	2	0	2
J.A.	26	F	1	Vasc., L	0	4	0	3	0	3
R.B.	54	M	1 w	Vasc., L	0	3	0	3	0	2
S.C.	46	F	4	Vasc., L	0	4	0	3	0	3
B.I.	55	M	4	Vasc., R	3	1	3	1	3	0
F.E.	53	F	1	Tumour, R	5	1	4	0	4	0

Vasc. = ischaemia or haemorrhage; L = left, R = right. Other abbreviations as in Table 1.

RESULTS AND DISCUSSION

As in Experiment 1, responses were considered correct when the prespecified keys were depressed and the sequence was tapped in the correct order. Responses shorter than 150 ms and longer than 3000 ms were excluded from analyses. Approximately 11% of the trials were classified as errors. An inspection of errors revealed no systematic tendencies. As in Experiment 1, RTs of correct responses were subjected to ANOVAs to assess sequence and position effects.

Average median T1 RTs, as a function of sequence length (L = 1 to L = 3) and hand (ipsilateral vs contralateral) are shown in Table 3. T1 RTs were subjected to an ANOVA with the within subjects factors hand and sequence length. Response

TABLE 3. SEQUENCE AND POSITION EFFECTS OF CEREBELLAR PATIENTS WITH UNILATERAL DISABILITY*

	Executing hand					
	Ipsilateral			*Contralateral*		
	T1	*T2*	*T3*	*T1*	*T2*	*T3*
Sequence length L = 1						
Mild disability	342			335		
Moderate disability	475			378		
Means	408			356		
Sequence length L = 2						
Mild disability	358	260		384	206	
Moderate disability	483	500		435	298	
Means	420	380		409	253	
Sequence length L = 3						
Mild disability	403	287	276	396	238	237
Moderate disability	467	557	498	460	377	338
Means	435	422	387	428	307	288

Patients with mild and moderate disability are listed separately. T1 = reaction time for the sequence initial response in ms; T2 and T3 = interval (in ms) between first and second responses and second and third responses, respectively.

onset time increased with sequence length and amounted to 383 ms, 415 ms, and 432 ms for sequences of L = 1, L = 2, and L = 3, respectively, $F(2,22) = 9.542$, $P < 0.001$. There was also a tendency towards shorter response onsets for contralateral responses (398 ms) than for ipsilateral responses (422 ms); this difference, however, failed to reach statistical significance, $F(1,11) = 2.096$, $P < 0.2$. More importantly, there was the predicted tendency towards a smaller sequence length effect for ipsilateral responses than for contralateral responses. The interaction of the factors hand and sequence length also failed to reach statistical significance, $F(2,22) = 2.194$, $P < 0.14$. The T1 data thus suggest cerebellar involvement in the execution of serial action, but the outcome of statistical tests does not warrant a firm conclusion.

A post hoc inspection of individual patient's T1 data was also consistent with the view that cerebellar structures are implicated in the control of serial movement execution. As in Experiment 1, the inspection showed that severity of cerebellar disease affected the magnitude of sequence length effects. Patients with mild unilateral cerebellar dysfunction showed sequence length effects for responses executed with contralateral and ipsilateral hands; patients with moderate unilateral cerebellar dysfunction, in contrast, showed a sequence length effect for responses executed with the intact contralateral hand but not for responses executed with the impaired ipsilateral hand. Following this inspection, we partitioned patients into 2 equal-size groups. One group of 6 patients suffering from relatively mild unilateral cerebellar disease and one group of 6 patients suffering from moderate unilateral cerebellar disease. Patients with average disability ratings of less than 2.0 (*see* Table 2) were classified as 'mildly' disabled and those with a disability rating of 2 or more as 'moderately' impaired. An ANOVA with the within-subjects factors hand and sequence length was applied to T1 RTs of each group.

The statistical comparison of T1 RTs in patients with mild and moderate disability shows a qualitatively different pattern of T1 RTs in the 2 patient groups (*see* Table 3). Patients with moderate cerebellar disability revealed shorter T1 RTs for responses executed with the unaffected contralateral hand than for responses executed with the affected ipsilateral hand, $F(1,5) = 4.144$, $P < 0.09$. Patients with mild cerebellar disability did not show significant T1 RT differences between affected and unaffected hands, $F < 1$. Furthermore, T1 RTs of patients with moderate cerebellar disability revealed a substantial sequence length effect for responses executed with the intact hand contralateral to the lesion but not for responses executed with the impaired hand ipsilateral to the lesion; the interaction of sequence length and executing hand was significant in this patient group, $F(2,10) = 5.504$, $P < 0.025$. T1 RTs of patients with mild cerebellar disability showed sequence length effects for ipsilateral and contralateral responses and the interaction of sequence length and executing hand was not significant, $F < 1$. The results of these post hoc analyses thus suggest that cerebellar structures are implicated in the execution of planned serial responses.

As in Experiment 1, position effects were assessed separately. RTs for sequence initial and noninitial responses, as a function of hand (ipsilateral vs contralateral) and response position (first, second (third, $L = 3$ sequences only)), are shown in Table 3. Separate analyses of variance with the 2 within subjects factors hand and response position were applied to $L = 2$ and $L = 3$ data of all 12 cerebellar patients. The results showed shorter $L = 2$ and $L = 3$ execution times when the intact contralateral hand was used than when the impaired ipsilateral hand was used, $F(1,11) = 4.466$, $P < 0.05$, and $F(1,11) = 11.455$, $P < 0.01$, respectively. $L = 2$ and $L = 3$ sequences also showed positive position effects with shorter interresponse times than response onset (T1) times, $F(1,11) = 18.697$, $P < 0.001$, and $F(2,22) = 7.219$, $P < 0.005$, respectively. As expected, the position effect was qualified by the laterality of the executing hand. Specifically, the positive position effect was larger for sequences executed with the contralateral hand than for responses executed with the ipsilateral hand; the interaction of the factors hand and response position was statistically significant in the $L = 2$ data, $F(1,11) = 9.230$, $P < 0.01$, and approached significance in the $L = 3$ data, $F(2,22) = 2.471$, $P < 0.1$.

An additional qualitative evaluation of position effects was informative in showing somewhat different position effects in mildly and moderately disabled patients. As shown in Table 3, mildly disabled patients revealed positive position effects for sequences executed with ipsilateral and contralateral hands. Moderately disabled patients also revealed positive position effects for sequences executed with the intact contralateral hand, but revealed negative position effects for sequences executed with the impaired ipsilateral hand.

To summarize, the results of Experiment 2 are consistent with the results of Experiment 1. As in Experiment 1, mild cerebellar dysfunction had negligible effects on sequence length and position effects. Moderate cerebellar dysfunction, in contrast, appeared to influence the two effects. Specifically, moderately impaired cerebellar patients with unilateral cerebellar disease revealed relatively normal sequence length and positive position effects for responses executed with the intact contralateral hand and a lack of a sequence length effect and negative position effects for responses executed with the impaired ipsilateral hand. This pattern of results cannot be attributed to global impairments which may affect the encoding of the reaction signal, to attention or alerting deficits, to memory impairments, or to extracerebellar damage, since each subject served as his/her own control. Consequently, the results of Experiment 2 are consistent with the hypothesis that cerebellar structures are used to translate motor programs into actions, possibly by setting response parameters for peripheral effectors which are involved in the execution of a sequence of responses.

GENERAL DISCUSSION

The speed, smoothness, and precision which characterizes the execution of practised sequential movements appears to follow the motor programming of all sequence constituents prior to response onset (Keele, 1968; Sternberg *et al.*, 1978; Rosenbaum *et al.*, 1984). Decomposition of complex movements, which is the hallmark of cerebellar disease (Holmes, 1917, 1939), suggests a cerebellar involvement in the execution of such programmed movements. Reviewing a number of studies, Brooks (1984*a*, *b*, *c*) concluded that the cerebellum controls the 'packaging of planned motor acts'. According to this view, the cerebellum acts like a 'clutch' between response planning and response execution, that is, before response onset, the cerebellum translates the intent of the individual into response parameters which control peripheral muscles. When cerebellar damage occurs, the temporal composition of an orderly timed sequence of a motor program with multiple functional subunits becomes deranged (Dichgans and Diener, 1984).

Evidence for this hypothesis has been derived primarily from the detailed study of agonist-antagonist interactions during individual movements. The current investigation tested whether cerebellar lesions also affect the execution of practised (and programmable) *sequences* of movements. Two groups of patients were studied. One group of 13 subjects had bilateral cerebellar disease and another group of 12 subjects had unilateral cerebellar disease. Using a paradigm developed by Sternberg *et al.* (1978), two separate indices of the efficiency of patients in translating programmed movement into action were obtained, consisting of the sequence length effect and the position effect. If cerebellar dysfunction prevented subjects from effectively translating a programmed sequence of responses into peripheral response parameters prior to response onset and obliged them instead to execute each element of a sequence of responses as a separate unit, then the time to initiate the execution of the sequence of responses should be unaffected by subsequent responses; i.e., no sequence length effect should occur. Furthermore, if cerebellar dysfunction prevented setting of response parameters for a group of responses before response onset then the normal facilitation of noninitial responses (relative to initial RTs) should be lost and each component should be a functionally independent unit, i.e., no positive position effect should be present or the positive position effect should be greatly reduced.

Three major comparisons were performed in the present sudy. First, patients with generalized cerebellar dysfunction were compared with neurologically unimpaired controls who had participated in an earlier study (Rafal *et al.*, 1987). Secondly, patients with mild bilateral cerebellar disability were compared with patients with moderate bilateral disability and, thirdly, patients with mild and moderate unilateral cerebellar lesions were studied comparing the performance of their clinically affected hand ipsilateral to the lesion with the performance of their clinically unaffected hand contralateral to the lesion. The pattern of results was highly consistent across all comparisons. Specifically, the results suggest that sequence length and positive position effects which characterize the performance of neurologically unimpaired subjects were absent when movements were executed with hands moderately affected by clinical disability from cerebellar dysfunction. These results could indicate that moderate cerebellar dysfunction prevents the translation of a programmed (or programmable) sequence of responses into action prior to response onset.

The current observations contrast strikingly with the performance of patients with Parkinson's disease who performed the identical sequential tapping task with movement sequences of L = 1 to L = 3 (Rafal *et al.*, 1987). In contrast to cerebellar patients, Parkinson's disease patients had slower response onset times than neurologically unimpaired control subjects, regardless of sequence length. Dysfunction of the basal ganglia thus affected some component of motor function. However, sequence length and position effects were nearly identical in patients with Parkinson's disease and control subjects. Consequently, disruption of the translation process that is used to transfer a motor program to the effector system, as it was found in the present study, is not the result of any CNS lesion affecting motor function. Other explanations of the present results, which attribute the absence of sequence length and position effects to general cognitive impairments of encoding operations, short-term memory capacity, readiness, or attention can also be excluded. In Experiment 2, each moderately impaired subject served as his/her own control so that any global impairment which affected ipsilateral responses would have equally affected contralateral responses. Nevertheless, laterality affected the execution of a sequence of planned manual responses. Sequence length and positive position effects were obtained when patients used their intact contralateral hand to execute response sequences, but both effects were absent when moderately impaired subjects used their impaired ipsilateral hand to execute the sequences.

Sternberg *et al.* (1978) proposed a specific model to account for the sequence length effect in the sequential tapping task. In their model, the parameters of each element of a sequence of responses are specified before response onset and all specified (and programmed) elements are loaded into a motor buffer. When the reaction signal is perceived, a serial and self-terminating search is made for the sequence initial response which, when accessed, is passed on to the effector system. As the length of the sequence increases, buffer search time increases, resulting in a linear sequence length effect. Position effects could accrue because fewer searches are performed for noninitial responses. An alternative model to account for the sequence length effect has been proposed by Rosenbaum (1985). According to Rosenbaum, a sequence of to-be-executed responses can be ordered along a time dimension. Once the delay between successive responses has been specified, the order of these responses is also determined. A motor program then consists of a *schedule* of successive motor events and motor programming is the process of determining which motor commands are to be employed and with which clock pulse they are to be associated. Executing a motor program is the process of allowing responses to be triggered when their associated clock pulses occur. Within this perspective, the magnitude of the sequence length effect reflects real time demands for the set-up of response schedules for peripheral muscle effector systems and the position effect reflects, at least in part, benefits due to the advance scheduling of noninitial responses. According to this model, the lack of sequence length and position effects in cerebellar patients with moderate dysfunction indicates an inability to schedule a sequence of successive motor events before movement onset.

The hypothesis that cerebellar disease disrupts the scheduling of a sequence of movements before movement onset agrees with recent studies which reveal specific timing deficits in cerebellar patients (Ivry, 1986). In this study, a quantitative analysis of the variability of successive finger tapping intervals (Wing and Kristofferson, 1973) was used to identify two components of response variability. One component which reflects peripheral variability, due to changes in force, finger position, limb or body movements and a second component which reflects variability of a central time keeper. Ivry's results indicate that the increased response variability of cerebellar patients is due to damage to the central time keeping mechanism. This timing mechanism may also control the scheduling of successive movement elements in the present study.

Our observations in human patients also agree with physiological studies in experimental animals. Unit recordings from dentate neurons revealed increased firing rates after a reaction signal occurred and before response onset; the intensity of the discharge correlated with RTs, suggesting that the neurons encode timing for movement onset (Lamarre *et al.*, 1983). A more direct demonstration of cerebellar involvement in the timing of programmed responses was provided by Hore and Vilis (1984). In their experiments, animals held a handle that loaded triceps. During the holding task, predictable and unpredictable perturbations were applied. An early antagonist response, which appeared to be synchronized to a torque pulse onset, occurred only for predictable perturbations. More critically, no early antagonist responses occurred for predictable perturbation during dentate cooling. Functional disconnection of the cerebellum thus resulted in the elimination of a time-locked predictive response component. Dentate recordings also support the notion that the cerebellum is involved in the planning of a sequence of movements. Robertson and Grimm (1975) trained 3 squirrel monkeys to execute a sequential button pressing task while 87 dentate neurons were recorded. The results showed some elevation in the discharge pattern of most dentate neurons for each button press response; in addition, the activation pattern of all dentate neurons increased somewhat on movement onset and increased for some neurons just before the sequence initial response.

The present results also raise a number of questions. First, patients with a mild cerebellar lesion showed relatively normal sequence length and position effects, even though they suffered from noticeable behavioural deficits during clinical examination. It is possible that mild cerebellar disease is more likely to be observed when response execution requires the use of a large number of muscle systems (e.g., grasping or pointing towards a target), as generally required in neurological examinations. When relatively few muscle systems are implicated in a response, as required in the present study, effects of mild cerebellar lesion might be negligible. Secondly, the present experiments cannot uniquely determine the mechanism which underlies the lack of a sequence length effect and the negative position effect in patients with a moderate cerebellar lesion. It could be possible, for example, that moderately impaired cerebellar patients are able to specify the temporal coordinates of a whole sequence of responses before response onset but may refrain from doing so, possibly because impaired peripheral feedback no longer signals that a previous response element has been executed. Thirdly, it could be argued that the results of Experiments 1 and 2 primarily reflect a disability in the execution of sequence initial responses. Impairment of the sequence initial response could eliminate sequence length effects and influence the execution of noninitial responses resulting in a negative position effect. Again, this view implies that patients with moderate cerebellar damage could translate a programmed sequence of responses into action parameters before response onset, but refrain from doing so because other disabilities render this strategy futile. Future research will be needed to assess the validity of these hypotheses.

In summary, converging evidence from human and animal studies indicates that a practised movement sequence is programmed before movement onset so that the sequence will be executed as a single fluid unit. The translation of a programmed sequence of responses into peripheral effector commands appears to occur only when a relatively intact cerebellar structure can be contacted. When the cerebellum is moderately disabled, the movement sequence becomes 'decomposed' and patients execute each element of the sequence as a functionally separate unit.

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DIRECT DYSLEXIA

PRESERVED ORAL READING OF REAL WORDS IN WERNICKE'S APHASIA

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SUMMARY

A 70-yr-old man was able to read aloud, without comprehending what he read, following a stroke that caused Wernicke's aphasia with severely impaired comprehension of speech. Tested on admission, and at 3 and 9 months, he could read aloud both orthographically simple and orthographically complex real words, and showed neither semantic errors, preference for nouns, nor difficulty with function words. He could not, however, read aloud orthographically simple nonwords. His disorder thus appears to be the first pure example of 'direct dyslexia', which, in contrast to previously well-documented examples of 'deep' and 'surface' dyslexia, implies the existence in reading of a direct route, independent of phonology or semantics, between visual and oral word representations.

INTRODUCTION

Acquired dyslexia has been characterized by linguistic criteria into two major syndromes, deep and surface dyslexia. Patients with deep dyslexia have difficulty with phonological processing, especially when reading nonwords or nonsense syllables (Coltheart, 1987; Coltheart *et al.*, 1987; Marshall and Newcombe, 1987). Performance on reading words aloud varies with part-of-speech. Nouns are read most easily, then adjectives, and then verbs; function words (e.g., prepositions, articles, or conjunctions) are especially difficult. Reading performance is also better with concrete or imageable nouns than with abstract nouns. Patients with deep dyslexia make semantic and inflectional errors, with substitution of a word of similar meaning or class (e.g., cow to horse). Semantic errors suggest at least partially preserved semantic comprehension; such patients may be able to match correctly pictures with words they can neither read aloud nor understand. These patients also make derivational errors: the substitution changes declension or conjugation through the suffix (marry to married) or by some other change (birth to born); and they make visual errors: the substituted word looks like the original

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(gallant to gallon; crowd to crown). Function words tend to be substituted for one another.

Patients with surface dyslexia can read aloud orthographically regular words and nonwords (and can thereby comprehend the former), presumably by grapheme-phoneme rules (using correspondences between letters or groups of letters and sounds), but cannot read orthographically irregular words correctly because of slavish application of these rules (Newcombe and Marshall, 1985). In reading 'tough', such patients might say 'to-ugh'. They show derivational and visual errors but do not make semantic errors.

Surface dyslexia can occur with or without aphasia. Deep dyslexia has always been reported in association with aphasic disorders. Particular aphasic symptoms (e.g., fluency, comprehension of speech, agraphia) do not predict the type of dyslexia. These dyslexic syndromes led to a model of two independent processing modules for normal reading: a direct (or visual) route from the visual word-form system to the semantic system, and a phonological route from the visual word-form system to phonological processing systems. In the direct route, words are interpreted as whole symbols, like Chinese ideograms; comprehension thus precedes verbalization. In the phonological route, letter symbols are converted to sounds in order to construct words; pronunciation precedes comprehension. The reference to ideograms is not gratuitous; deep and surface dyslexia have occurred in Japanese patients with selective difficulty in reading either the ideographic (kanji) or phonetic (kana) symbols of Japanese writing (Sasanuma, 1987).

Loss of one processing route with complete preservation of the other does not, however, readily explain all the features of deep or surface dyslexia. In particular, the presence in deep dyslexia of semantic errors and dissociated impairment of concrete and abstract nouns and parts of speech has implied to some workers a disturbance in the semantic route itself (in addition to the more severe disruption of the phonological route). Such a view received support from a case of so-called 'phonological dyslexia' (Beauvois and Dérouésne, 1979), in which there was inability to read aloud nonwords, yet, in contrast to deep dyslexia, real words were read without semantic errors and without regard to orthographic complexity, concreteness, or part of speech. The syndrome was interpreted as a more pure or 'single component' form of deep dyslexia. A problem with this syndrome was that as further cases were reported, considerable variability among them became apparent. As noted in a review of 15 patients said to have phonological dyslexia (Sartori *et al.*, 1984), nonword reading ability ranged from zero to 80% correct and word reading from 40 to 100%; reading comprehension was considered intact in some (especially when tested with matching tasks) but impaired (or not systematically tested) in others.

Schwartz *et al.* (1979) described a patient who could not understand what she read, even with matching tests; she could, however, read aloud real words regardless of their orthographic complexity as well as some nonwords. Unlike patients with phonological dyslexia, this patient's ability to read aloud could not be attributed to partially preserved semantic understanding of what she read. She therefore provided 'evidence for the role of word-specific print-to-sound associations in reading'. A third processing route, independent of either phonological or semantic access, was postulated to account for reading aloud real words, especially when orthographically irregular. Preservation of this 'direct (route) between visual and oral word-representations' in patients with damage to the semantic and phonological routes would produce, as Newcombe and Marshall (1981) called it, 'direct dyslexia'.

By this formulation, however, the patient described by Schwartz *et al.* was not a pure case, for she could read nonwords and had a tendency to regularize orthographically irregular words, demonstrating that her phonological route was functional. To our knowledge a truly prototypical case of direct dyslexia has not yet been reported. We were therefore interested to encounter a patient with pure direct dyslexia in association with Wernicke's aphasia.

CASE REPORT

G.H., a 70-yr-old right-handed man, was brought to the emergency room in July 1985 by his wife, who stated that he had been speaking nonsense for a month. She noted that his problem had been of sudden onset, but that his mental functioning had already been deteriorating over several months. She could not give more precise details.

On admission, he had aphasia characterized by fluent prosodic speech that consisted of real words but made no sense. Comprehension of speech, naming, repetition, writing, and reading were severely impaired as detailed below. He had a short-stepped gait, but neurological examination was otherwise normal with no cranial nerve, motor, sensory, or reflex asymmetries. The admitting diagnoses were dementia and stroke with Wernicke's aphasia. Normal studies included complete blood count, urinalysis, and serum sodium, potassium, vitamin B12, and calcium, as well as liver and thyroid function tests, ECG, and chest x-ray. An EEG showed diffuse slowing with no asymmetry. A CI scan (fig. 1) showed lucencies compatible with infarction in the left frontal and temporal lobes, including the planum temporale.

The patient had been schooled through the sixth grade in South Carolina. He had worked at a variety of manual jobs. Until the year before admission, he had read the New York Daily News thoroughly every day.

RESULTS

In addition to the admission examination, the patient received more extensive language evaluation at 3 months and 9 months following admission. We followed the format of the Boston Diagnostic Aphasia Examination where applicable, and supplemented it with other material designed to elucidate his reading abilities.

At all times, speech was fluent and prosodic. At 3 months his output was limited to stock phrases that he would repeat with minor variations: 'That was beautiful.' 'You're looking real good today.' He had few literal paraphasias and no verbal paraphasias but would frequently lapse into mumbling. At 9 months his output showed more variety as well as more literal paraphasias; at times his speech even

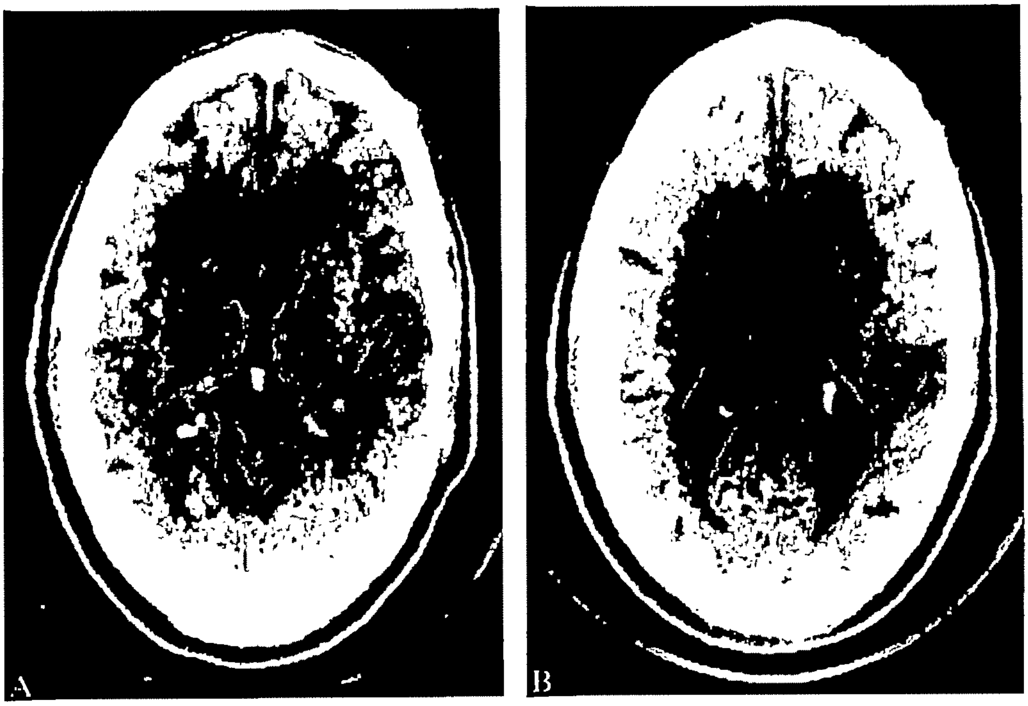

Fig. 1. A and B, computerized tomography of the head (without contrast). Seen in each slice are (1) frontal periventricular lucencies, on the left extending posteriorly across the corona radiata; (2) left temporal lobe lucency affecting both cortex and white matter, including posterior superior temporal gyrus (planum temporale); and (3) diffuse ventricular enlargement and sulcal widening, greater on the left.

became jargon: 'Affa, affa, belba-buract-no this was clined in case yekaleg-no it was all-I didn't hef it-no sir.'

Speech comprehension was always moderately to severely impaired. At 3 months, he followed a few simple commands on only one occasion, quickly lapsing into perseveration. On subsequent days he followed no commands. At 9 months, he followed simple commands fairly consistently, although he still perseverated after 4 or 5 correct executions such as protruding his tongue, raising his arm, standing, sitting, and touching various body parts. He was unable to identify named objects other than body parts. He never followed a two-step command but would generally do only the first part of it, and he did not answer simple yes-no questions appropriately. When asked 'Am I wearing a hat?' he touched the top of his head. He would sometimes simply repeat the question with appropriate grammatical alteration. For example, asked 'Is this your nose?' he said 'Is this my nose?' With continued questioning he would respond in jargon speech.

At 3 months he repeated some single words but mostly he would not repeat at all. Repetition of foreign phrases (i.e., for him nonwords) was impaired to the same degree as repetition of phrases in English. At 9 months, repetition came more readily but was riddled with paraphasias. ‘The man went home’ elicited dissimilar jargon. ‘Wristwatch’ became ‘wrist balda fide’; ’New York City’—‘New York Kitty pity’; ‘The president lives in Washington’—‘Pres-president in fensy in práct’, then ‘Presidi in precifice in prensy’.

Naming on admission was circumlocutory but without paraphasias. Shown matches, he said ‘This is for cigarettes.’ Candy—‘It’s a treat, you eat it’. Examined at 3 months, he did not appear to understand the task and did not name anything to command or spontaneously. Shown a picture of a house he said ‘two floors’. At 9 months, naming was neologistic: ‘kalleej’ for hand; ‘u’ for pen.

Soon after admission, asked to write ‘I am in the hospital’ to dictation, he wrote ‘cam I am a am’. At 3 months, he copied single words and wrote his name spontaneously but wrote nothing to dictation. At 9 months he wrote his name to command and then perseverated, writing his name when asked to write other words. Later, he wrote ‘cat’ and ‘dog’ to dictation. For ‘New York’ he wrote ‘new new’. For ‘tough’ he wrote ‘cap’; he was able to copy writing in capital printing but not in lower case script.

Oral reading was generally correct for words or short phrases. At 3 months he easily named single letters and read the words of section IIa of the Boston Diagnostic Aphasia Examination (Appendix 1) without error. He read list IIIa with only 2 errors, saying ‘Mammy’ for ‘Mama’ and slurring ‘huckleberry’.

Further examination was directed at determining whether he read phonetically or semantically. On reading different kinds of real words, he made infrequent errors, all either derivational or visual. For example, he read a list (Appendix 2) of 10 orthographically complex words (words that cannot be sounded out) with one error—saying ‘hăsty’ for ‘hasty’. Given a list (Appendix 3, A and B) of 20 3-letter nouns, he made only 3 errors: ‘carna’ for ‘car’, corrected with prompting; ‘zeg’ then ‘zug’ for ‘zoo’; and ‘intense’ for ‘ant’. On 20 nonrepresentational nouns (3-C), he made 4 errors: ‘cave’ for ‘eve’, ‘rip’ for ‘rap’, ‘i-r-e’ (spelling word) for ‘ire’, and ‘gig’ for ‘jig’. On 20 non-nouns (3-D), the 4 errors were as follows: ‘u-j, u-linging’ for ‘ugh’ ‘couch’ for ‘coy’, ‘on’ for ‘one’, ‘āgo’ for ‘ago’. On the other hand, given 20 nonsense words (3-E) he correctly read only 3, and he read even these with uncharacteristic hesitation. Generally, presented with a nonword, he would remain silent. This was in marked contrast to his behaviour with real word reading when he would respond promptly and seem eager. If pressed for a response, he would spell out the word or decompose it into a letter and a 2-letter word. In two cases, he tried to make real words out of nonwords, giving ‘cafe’ for ‘caf’ and saying ‘When I looked at the eggs on the table’ for ‘heg’. On each occasion, following the testing for nonword reading, he was able to read real words with the same degree of proficiency as before. He was also able to read sentences. Shown ‘No ifs and or buts’, he initially read ‘No fits or buts’, but then read it correctly when asked to read it again. He was able to read Gray reading selection 1 (Appendix 4) rapidly with only a few errors, saying ‘body’ for ‘boy’ in one place and ‘dog’ for ‘boy’ in another, ‘tie’ for ‘cry’, and ‘can’t’ for ‘cannot’. After reading this selection on one occasion, he spontaneously added 'He probably wanted the dog to go home.'

Reading comprehension was severely limited. On testing at 3 months, on the same day that he followed a few verbal commands, he also followed several simple written commands after reading them aloud. Thereafter he never appeared to comprehend any. On examination at 3 months attempts were made to engage the patient in a variety of matching tasks, including verbal to written, picture to written, object to written, and the converse of each of these. Despite being attentive, he showed no understanding of what was required of him. When pressed, he seemed aware that some choice was required from among the objects or words placed before him but his choices were no better than random. At 9 months, he read aloud simple commands correctly without following them. Reading 'Am I wearing a hat?' he touched the top of his head. He again failed to perform any matching tasks.

He was able to read numbers easily, both single digits and numbers in the tens and hundreds, sometimes interpolating 'dollar' as if he were reading a price. He was also generally successful in reading time off a clock face drawn without numbers, making the correct distinction between the hour and the minute hand.

Two years later he was reexamined in a nursing home. Receiving thiothixene and benztropine for agitation, he had parkinsonian bradykinesia and a stooped gait. Although cooperative and docile, he made little eye contact, had no spontaneous speech except when queried, and had great difficulty getting the gist of nonverbal instructions. Speech was still fluent and prosodic, with considerable literal paraphasic contamination ('You got a wa wa eso jo sa ringsa day'). He followed no commands and did not indicate affirmative or negative to yes-no questions. Object naming and repetition testing produced several syllables of literal jargon; it was unclear if he was actually trying to name or repeat. He made no attempt to read or write.

DISCUSSION

The most striking feature of this patient's dyslexia was his preserved ability to read real words, whether orthographically regular or irregular, in the presence of (1) severe Wernicke's aphasia, and (2) inability either to read aloud nonwords or to comprehend what he read. His lack of reading comprehension appeared total; he failed at matching words with pictures and made no semantic errors. When reading aloud, he showed no preference for concrete over abstract nouns or for nouns over other parts of speech, including function words. He made rare derivational and functional errors. Although his reading of nonwords gradually improved, he never read them correctly; conversely, the real words he missed were uncommon (e.g., 'ire', 'coy') and may not have been part of his vocabulary.

Previous reports of preserved reading in aphasia have usually involved patients with intact reading comprehension in the setting of impaired comprehension of speech. Sevush *et al.* (1983) reported 2 patients who showed this dissociation. Their first patient, a 53-yr-old man, presented with aphasia, right hemiparesis, and right homonymous hemianopia. On examination one year later he had paraphasias on spontaneous speech and poor repetition and naming. Comprehension was also impaired although intact for simple phrases. His writing showed word substitutions. Reading was said to be 'slow and effortful' but his comprehension of what he read was better than his comprehension of spoken speech. His oral reading was also considered better than his spontaneous speech, showing fewer paraphasic errors. His reading showed the stigmata of surface dyslexia, with characteristic mispronunciations of orthographically irregular words. The second patient, a man of the same age without hemiparesis or visual field loss, had Wernicke's aphasia with profoundly impaired speech comprehension. Reading comprehension, however, was intact for sentences, and reading aloud produced less jargon and paraphasias than did spontaneous speech.

Hier and Mohr (1977) reported a 28-yr-old man with Wernicke's aphasia after encephalitis. He could write names that he could not say and, although unable to read aloud, understood written language better than speech.

Heilman *et al.* (1979) reported 3 similar patients, although only 1 had fluent speech. This patient, a 60-yr-old man, had aphasia, visual field loss, and mild right hemiparesis. Speech contained paraphasias; naming, repetition, and auditory comprehension were poor. Reading comprehension was somewhat better. Oral reading was not directly compared with spontaneous speech. The patient was able to read both words and nonwords and employ phonetic values in rhyme and meaning matching tests.

The patients of Sevush *et al.* and Heilman *et al.* thus had Wernicke's aphasia with relatively preserved reading comprehension and oral reading of words and nonwords. Hier and Mohr's patient had Wernicke's aphasia with loss of ability to read aloud but relatively preserved reading comprehension. In contrast to these patients, our patient had Wernicke's aphasia with preserved oral reading of real words but loss of reading comprehension and inability to read nonwords.

Reading aloud is a form of repetition, involving phonetic reproduction of speech input from a visual rather than an auditory source. Our patient and those of Sevush *et al.* and Heilman *et al.* had difficulty with auditory repetition; their reading abilities cannot be a result of preservation of this function. Nonetheless, reading could improve speech by providing a constant external check for both phonology and semantics, in contrast to spontaneous speech in which any such check must be entirely internal. The patients of Sevush *et al.* and of Heilman *et al.* had access in their reading to information both phonological (with intact reading of nonwords) and semantic (with relatively preserved reading comprehension). Such information would be essential in the feedback role of reading aloud. Our patient had no access to such information, yet he could read aloud only real words. It must be presumed, therefore, that he was using a processing route that led directly from visual to oral real-word representations, bypassing both semantics and phonetics.

As noted, the existence of such a route was first suggested by Schwartz *et al.* (1987). In an earlier report, their patient, a 62-yr-old woman, was described as having a progressive dementing illness with fluent speech, severely impaired confrontational naming and speech comprehension, and relatively preserved oral repetition (i.e., transcortical sensory aphasia) (Schwartz *et al.*, 1979). It was further observed that her speech and speech comprehension displayed relative preservation of syntactic compared with semantic processing. Moreover, she could read aloud both words (regular and irregular) and nonwords. In their later report the authors found this ability to be associated with total lack of reading comprehension (as shown by random performance on picture-matching and categorical word-sorting, as well as absence of semantic errors). The authors speculated that in reading she was employing 'a more direct lexical mechanism, one which proceeds directly from visual word form (visual input logogen) to a stored representation in a phonological lexicon (output logogen)'.

In a psycholinguistic classification of acquired dyslexia, Newcombe and Marshall (1981) offered a block diagram, reproduced here in fig. 2, that recognized the existence of these direct, semantically-independent word-specific associations between print and sound ('barking at print'). Deep dyslexia would result when there was disruption of routes C ('grapheme-phoneme correspondence rules') and B ('direct association between visual and oral word representations'), with reading then depending solely on route A ('lexical semantic representations'). Surface dyslexia would occur with disruption of routes A and B. Theoretically, there should then exist a 'direct dyslexia', resulting from disruption of routes A and C. The authors pointed out that the case of Schwartz *et al.* was not a pure example of direct dyslexia, for her ability to read nonwords and her tendency to 'regularize' orthographically irregular words showed that she was still using route C.

Lebrun and Devreux (1984) also observed a patient with fluent aphasia who read sentences aloud without comprehension, but further details were not given. Glass *et al.* (1973) described 4 patients with global aphasia who were able to make written word/nonword distinctions of a sorting task despite being unable to do picture/written word matching. These patients provide further evidence for the existence of word knowledge independent of semantic knowledge. They might be thought of as showing a direct dyslexia masked by their aphasia and illustrate the importance of examining a patient's reading abilities in the context of overall language ability.

Our patient is the first to fit the model of direct dyslexia as predicated by Newcombe and Marshall, and his retained ability to read real words aloud offers further evidence for the existence of direct, semantically independent 'word-specific print-to-sound associations'. No anatomical conclusions can be drawn from his dissociated language abilities. (Although the history and CT scan suggested left cerebral ischaemia, his earlier history suggested the intriguing possibility that, like

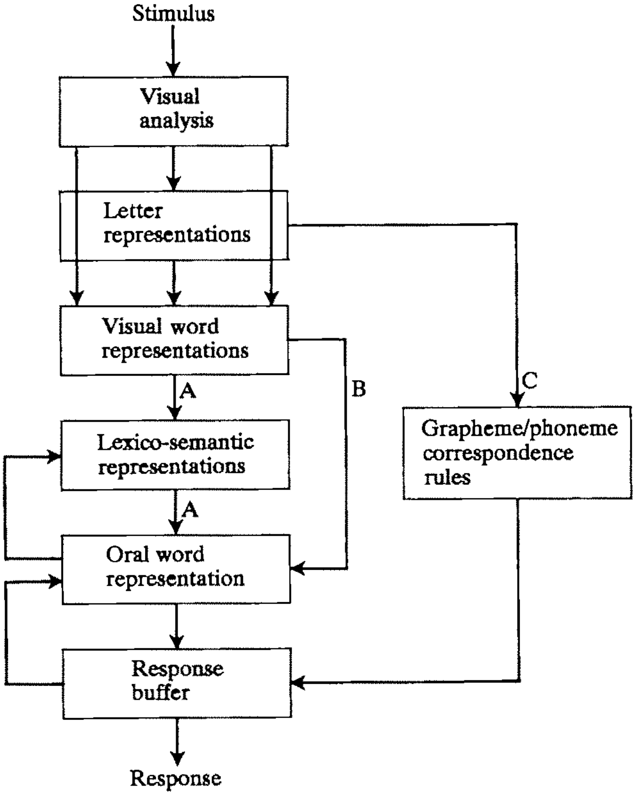

Fig. 2. Diagram representing different routes in reading. Deep dyslexia would follow damage to routes C and B; surface dyslexia would follow damage to routes A and B; direct dyslexia would follow damage to routes A and C. (From Newcombe and Marshall, 1981, reprinted by permission of the Orton Dyslexia Society.)

the patient of Schwartz *et al.*, he also had a more diffuse dementing illness, but historical details were not available. When last examined, 2 yrs later, his mentation had deteriorated, but he was receiving neuroleptic and anticholinergic drugs at the time.) Indeed, it should be emphasized that the dyslexic models of Newcombe and Marshall are psycholinguistic, not anatomical or physiological, and at present do not readily account for such phenomena as semantic paraphasias in deep dyslexia (or their absence in 'phonological dyslexia'), difficulty with abstract as compared to concrete nouns and with function words, and visual or derivational errors (Shallice and Warrington, 1987). Neither do they explain unusual syndromes such as 'semantic access dyslexia' (Warrington and Shallice, 1979), 'concrete word dyslexia' (Shallice, 1981), or 'word-form dyslexia' (Warrington and Shallice, 1980). As Newcombe and Marshall pointed out, there is a need 'to provide explanatory accounts of the patients and symptoms that appear to have no obvious interpretation within the confines of our current block diagrams. It may well turn out that as we attempt that enterprise . . . much of our current framework will have to be dispensed with.'

The development of an alternate model of cognitive processes, namely parallel distributed processing (McClelland, 1986; McClelland *et al.*, 1986; Sejnowski and Rosenberg, 1987) suggests new ways to look at language disorders. Rather than exploring dyslexia in isolation, it might be more profitable to consider a dyslexia in the setting of any accompanying aphasia and develop models that would help explain the patient's entire disability. In parallel distributed processing models, the various aspects of language processing—semantic, linguistic, phonetic and others—are not represented in distinct isolated modules but are represented to various extents in small independent neuron-like processing units. Instead of looking at the deficits that result when a single module is removed, one observes the residual function of which a network is capable after particular areas have been damaged. Thus G.H.'s 'dyslexia' may be best described as a 'lexia', a standing relic among extensive ruins.

In G.H.'s case, fluency and failure of comprehension are two attributes that are common to both his reading and his spontaneous output and auditory language processing. Interestingly but not surprisingly, the fluctuations in his comprehension affected both his reading and his oral comprehension at the same time. In fact, during the course of a single examination he showed identical behaviour (touching his head) when first reading and then being asked orally whether the examiner was wearing a hat. Although we did not see any evidence of parallel fluctuation in his degree of fluency, his greater tendency to paraphasias in his spontaneous speech on examination at 9 months was matched by his tendency to add phrases of jargon when he read aloud either words or nonwords. On the other hand his inability to read nonwords was not matched by particular difficulty in repeating nonwords presented orally.

In presenting G.H.'s case, we have attempted to show how his language disorder compares with those of other reported patients and how it might be described in terms both of modular and distributed models of language process. This case confirms a prediction made on the basis of the modular model and therefore provides evidence in favour of that model. On the other hand, newer modelling techniques may provide opportunities to explore language problems on a broader scale. Perhaps both modelling paradigms will prove to be complementary in elucidating the mechanisms of brain function.

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APPENDIX 1

(*Word lists from the Boston Diagnostic Aphasia Examination*)

IIA	*IIIA*
CHAIR	MAMA
CIRCLE	TIP-TOP
HAMMOCK	FIFTY-FIFTY
TRIANGLE	THANKS
FIFTEEN	HUCKLEBERRY
PURPLE	BASEBALL PLAYER
SEVEN-TWENTY-ONE	CATERPILLAR
DRIPPING	
BROWN	
SMOKING	

APPENDIX 2

(*Orthographically difficult words*)

TOWEL
KNOCK
CAUGHT
CHANCE
KNEE
HASTY
WASTE
HALF
THOUGHT
TOUGH

APPENDIX 3

(*Taken from Rosenberger et al., 1968*)

A	*B*	*C*	*D*	*E*
CAR	JUG	NAP	AGO	ZOJ
BEE	EGG	LOT	YES	CIJ
MAN	BAG	ONE	BUT	YUD
HOE	FAN	JIG	ONE	FET
BUG	NUT	PAR	COY	HEG
ZOO	DAM	IRE	UGH	GIX
HUT	APE	RAP	DUE	GOX
EAR	KEY	HIT	TOO	LAJ
BOX	SUN	SUM	ERR	CAF
CAT	PEN	GAP	SAD	KAP
HEN	RAT	TON	FAR	ZIF
COW	HAM	FUN	PRY	CEF
HAT	MAP	VIM	GET	YIL
PIE	ICE	EVE	OLD	DAX
AXE	GUN	CUT	HOT	WUB
DOG	ANT	BET	NOT	GAH
SAW	CAN	WAR	IRK	VUK
BOY	TUB	ART	MET	JOX
PIG	VAN	DIP	JAB	TOV
BED	WIG	ZIP	LOW	MEC

APPENDIX 4

(*Selection 1 from Standardized Oral Reading Paragraphs by William S. Gray, Services for Professional Educators, 5341 Industrial Oaks Blvd., Austin, Texas 78735*)

A boy had a dog.
The dog ran into the woods.
The boy ran after the dog.
He wanted the dog to go home.
But the dog would not go home.
The little boy said,
'I cannot go home without my dog'.
Then the boy began to cry.

Brain (1989), **112**, 595-620

OBSERVATIONS DURING TRANSIENT GLOBAL AMNESIA

A BEHAVIOURAL AND NEUROPSYCHOLOGICAL STUDY OF FIVE CASES

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SUMMARY

The clinical and behavioural features of 5 patients examined during transient global amnesia (TGA) are described. All underwent extensive neuropsychological testing during and sequentially after the attack. Our results show that in TGA there is a characteristic neuropsychological deficit which parallels that in the permanent amnesic syndrome. Personality, complex cognition and problem solving, semantic knowledge, language and visuospatial function remained intact. Immediate memory was preserved. Longer-term verbal and nonverbal memory was severely disrupted in all cases. In contrast, the extent of retrograde amnesia was highly variable. A famous faces test showed an extensive deficit in 3 cases, with improvement in all cases following the attack. Analysis of group data confirmed the presence of a reversible temporal gradient, in that more distant memories were relatively spared. On a famous events test, recognition was normal across all decades, but dating of events from the 1960s and 1970s was consistently impaired. The Crovitz test of remote personal episodic memory was given to 3 subjects; all showed impaired uncued autobiographical memory and in contrast to normal controls, had a virtual absence of recent memories.

During recovery from TGA there was progressive shrinkage of retrograde amnesia but a permanent short retrograde gap of around 1 h remained in all cases. Although subjectively normal within 24 h, all cases demonstrated persisting impairment of new learning for at least a week post-TGA.

The relevance of the neuropsychological data to theories concerning the amnesic syndrome is discussed. We postulate a temporary deficit in retrieval of remote memories which appears to be dissociable from the anterograde amnesia.

INTRODUCTION

The behavioural and neuropsychological features of transient global amnesia (TGA) have received little attention. Concepts of human memory and amnesia are based on the study of patients with permanent memory impairment, and there are many unresolved and controversial issues in this area which could be addressed

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by the study of patients with TGA, since the latter provides the opportunity to examine subjects both during and after an episode of dense amnesia.

The term TGA was first introduced by Fisher and Adams (1964) to describe a characteristic clinical syndrome of temporary amnesia, without accompanying focal neurological features, usually occurring in the elderly. Before 1964 the syndrome was undoubtedly recognized and reported under other titles (Bender 1956, 1960; Guyotat and Gourjon, 1956). The attacks, as described by witnesses, begin with the abrupt onset of amnesia and confusion often with repetitive questioning. Behaviour appears normal in other respects. Memory is severely impaired. After a few hours memory returns, except for a dense amnesic gap for the duration of the attack.

The literature now includes well over 500 reported cases (Markowitsch, 1983; Caplan, 1985). However, the cause of TGA remains unclear. Fisher and Adams (1964) favoured an epileptic aetiology. The majority of subsequent authors have proposed a cerebrovascular aetiology. More recent hypotheses include migraine (Caplan *et al.*, 1981; Crowell *et al.*, 1984) and mild head injury (Haas and Ross, 1986). The observed details in many reports are scanty and it is clear that much of the controversy regarding the aetiology of TGA has arisen because of looseness in the application of the term TGA and the lack of established diagnostic criteria (Caplan, 1985). Since the early precise descriptions, some authors have applied the term to a wide variety of different clinical situations merely sharing the feature of prominent memory loss. In keeping with the criteria proposed by Caplan (1985), we reserve the term TGA for witnessed attacks of definite amnesia without disturbance of consciousness, focal neurological deficits or ictal features, resolving within 24 h.

There have been only 5 reports of neuropsychological testing during TGA. Although a number of earlier authors provided detailed clinical descriptions of attacks (Fisher and Adams, 1964; Patten, 1971; Shuttleworth and Wise, 1973; Gordon and Marin, 1979), Wilson *et al.* (1980) were the first to report detailed quantitative neuropsychological observations, in a single case report. Data from 4 further cases have since been published (Caffarra *et al.*, 1981; Regard and Landis, 1984; Gallassi *et al.*, 1986). These studies have established that immediate memory (e.g., digit span) is preserved during TGA. Longer-term verbal learning (word list and story recall) is profoundly impaired. Memory for nonverbal material has been less thoroughly explored, but appears equally affected. General cognition and language are seemingly normal but have not been studied in detail. In addition, there is evidence that subclinical memory deficits persist for some time postattack. Regard and Landis (1984) found that verbal recall was still defective at 72 h. A similar pattern of delayed recovery was noted by Gallassi *et al.* (1986), whereas Caffarra *et al.* (1981) found that verbal memory was significantly impaired at 6 months.

The case studies cited above have all concentrated on anterograde memory. Informal estimates of the length of retrograde amnesia have varied from a few days (Wilson *et al.*, 1980; Gallassi *et al.*, 1986), and several months (Regard and Landis, 1984) to 30 or more years (Gordon and Marin, 1979; Caffarra *et al.*, 1981). The only report of formal remote memory testing during TGA is that by Wilson *et al.* (1980), whose subject performed normally on Albert's Remote Memory Questionnaire, both during and after the amnesic episode. Regard and Landis (1984) stated that their 2 subjects recognized and named famous faces normally, although data were not presented. Several authors have drawn attention to the fact that during TGA, subjects exhibit particular difficulty in recalling the order of past memories and events. This chronological confusion was first noted by Caffarra *et al.* (1981). Regard and Landis (1984) and Gallassi *et al.* (1986) also commented upon defective chronological judgement, which remained evident for 48 h postattack. No formal assessment of dating capacity during TGA has been reported.

Four important questions remain unanswered: First, is TGA purely an amnesic state, is it truly global and, in particular, is memory for verbal and nonverbal material equally affected in all cases? Secondly, what is the extent and pattern of retrograde amnesia? The question of whether a temporal gradient, with sparing of more distant memories, is an integral part of the amnesic syndrome remains controversial (Hirst, 1982; Weiskrantz, 1985). In permanently amnesic patients with remote memory loss it is not possible to distingush between deficits in acquisition and retrieval of information. TGA provides an opportunity to compare patients during and after an attack, and thus enables the extent of remote memory loss in the attack to be verified. If a reversible temporal gradient were demonstrated, it would have implications for models of amnesia in general. Thirdly, what is the relationship between the severity of anterograde and retrograde amnesia? This question addresses the issue of whether a common cognitive process underlies the encoding of new memories and the retrieval of remote memories. Finally, how quickly and fully does memory recover following TGA?

SUBJECTS

Patients

The 5 patients were all seen in the Neurology Department at the Radcliffe Infirmary between 1984 and 1986. All neuropsychological testing was performed by J. H. Patients underwent neurological examination, were questioned systematically about recent life events and news items, and were given a semistructured autobiographical interview. The informal estimate of retrograde amnesia was based upon this information. All interviews were video-recorded. Whenever possible, patients were seen and retested at 24 h, 1 wk, 4 wks, and 6 months postattack.

Normal controls

For the purpose of the study, the neuropsychological test battery (with the exception of the aphasia tests for which published normal data were used) was administered to 50 age-matched healthy control subjects. They were selected at random from local general practitioners' age/sex registers and were invited to participate in the study. The group consisted of 29 men and 21 women;

(range 47–82) mean age 64.5±8.6 yrs. The test results were grouped together since there were no significant differences between the sexes.

NEUROPSYCHOLOGICAL TESTING

The following battery of neuropsychological tests was administered.

Language

1. Confrontational naming, body part identification and 'Cookie Jar' picture description were tested, as standardized in the Boston Diagnostic Aphasia Examination (BDAE: Goodglass and Kaplan, 1983).

2. Verbal fluency: subjects were asked to produce as many words as possible, beginning with a given letter in 1 min. Three letters were used (F, A, S), as described by Benton and Hamsher (1978).

Problem solving

The task used was a modification of the 'Twenty Questions' test (Laine and Butters, 1982; Butters, 1985). Subjects were shown a sheet with 24 outlined drawings of objects arranged in a 6×4 matrix and asked to work out which object the examiner was thinking of at the time. The subjects could ask any question but the examiner could answer with only a yes or no response. The goal was to identify the preselected item with as few questions as possible. Three trials were given. The first 5 questions per item were classified as (1) *constraint seeking questions*, which significantly reduce the number of possible object alternatives (e.g., 'Is it in the top row?', 'Is it living?', or 'Is it a tool?'); (2) *pseudoconstraint seeking questions*, which superficially seem to be general questions but actually refer to only one object (e.g., the scissors 'Is it something that cuts paper?'; or (3) *specific questions*, which refer to a single object (e.g., 'Is it the saw?').

Memory tests

Immediate (short-term) memory tests

These consisted of (1) digits forward and backwards (Wechsler, 1981); and (2) Corsi block tapping span (Corsi, 1972).

Verbal memory tests

The following tests were performed. (1) Paragraph (story) recall. (2) Paired Associate Learning (PALT); immediate and 30 min delayed recall of both was tested. The material used was taken from the Wechsler Memory Scale (Wechsler, 1944) and different equivalent forms were used when retesting.

Drilled Word List Learning Test (Weintraub and Mesulam, 1985)

The subject was first drilled to a criterion of three correct trials. The word list was read at one word every 2 s. Immediately after the first trial the subject was asked to recall the list. The entire list was repeated until correctly recalled on three consecutive trials. Recall was then tested after 60 s *without* distraction, then after a further 60 s, 3 min and 10 min *with* distraction. Failures at 60 s and 3 min were followed by repeat drilling to criterion. Due to the severity of memory deficit during TGA a six-word list was used. On subsequent testing a different eight-word list was employed.

Nonverbal memory tests

Corsi block supraspan learning. Subjects were required to learn a block tapping sequence which exceeded their span by two blocks, to a criterion of two correct runs (De Renzi *et al.*, 1977).

Rey-Osterrieth complex figure. Copying ability and free recall at 30 min were tested (Osterrieth, 1944). Equivalent forms were used for retesting.

Incidental spatial memory test. Based on the method of Smith and Milner (1981), 16 toys were used, arranged randomly on a 60 cm board. The subject was asked to name each toy and to estimate the price of the real item represented by the toy; 10 s were allowed per item. On finishing the pricing, the subject was seated with his back to the board and distracted by a counting task. Meanwhile the examiner removed the toys from the board and covered it with a sheet of paper. After 4 min the subject was asked to recall as many toys as possible in 1 min (object identity recall). Then he was given the 16 toys and asked to replace them in their original positions(object location recall). The displacement was measured as the distance between the position assigned during recall and its original position.

Remote memory tests

Famous faces test. This was based on the famous faces tests of Sanders and Warrington (1971) and Albert *et al.* (1979). Photographs of prominent public figures who remained famous for approximately one decade, in the period 1920 to 1980, were used. The distribution was: 1930s—18; 1940s—18; 1950s—18; 1960s—17; 1970s—17. For each subject we excluded test items from decades before the subject reached the age of 15. The date of birth of the five TGA patients ranged from 1913 to 1937. The earliest decade considered therefore varied from the 1930s to the 1950s. Photographs were obtained from local newspaper archives and included politicians and statesmen, stage, film and television actors, singers and musicians, members of the Royal Family, sportsmen and record breakers. There was an even distribution of categories across the decades. The photographs were presented so that each block of ten contained photographs from all decades. The subject was asked to name the famous person. Cueing was not used.

Famous events test. Fifty famous public events from the period 1930-1980 were selected from a variety of published annual news reviews and historical literature. Clearly datable items of equal prominence were chosen (e.g., The Berlin Airlift, The Mau Mau, The Profumo Affair, The Watergate Scandal, etc.), based on a preliminary investigation of normal controls using a larger bank of events. The test consisted of 50 real items (10 per decade from the 1930s-1970s) and 50 fictitious items, made up to sound like real news events (e.g., 'The Ankara Agreement', 'The Jin Jin', 'The Goldberg Affair', 'The Blackheath Murders'). Real and fictitious items were mixed in a pseudorandom order so that each block of 10 items contained one news item from each decade, but in differing orders and with a varying number of intervening fictitious items.

The test was administered in two stages. (1) *Recognition.* Subjects were read each item in turn and then asked to signify those items remembered as real events. They were told beforehand that the list contained a mixture of real news items spanning 50 years and fictitious items. The first two in the list were false ('The Summerville Scandal' and 'The Barnsley March'). If the subject identified these as real then the correct answer was given and the instructions repeated. No subsequent help was given. (2) *Dating.* Whenever subjects identified an event as real they were required to assign it to a single decade.

Personal remote memory (modified Crovitz) test. The test was based on the method of Crovitz and Schiffman (1974) as modified by Zola-Morgan *et al.* (1983), and subsequently by Sagar *et al.* (1988). Subjects were asked to relate personally experienced life events from any time-period evoked by each of 10 high-frequency nouns (birds, tree, car, etc.) and then to estimate the date of the memory produced. A demonstration trial item was given before the test list. Instructions were repeated before each item. Subjects were given up to 4 min to respond, including, if necessary, 2 min with specific cues. During the first 2 min the examiner provided nonspecific prompts (e.g., 'Tell me more'). If after 2 min no episode was produced the examiner cued the subject by suggesting concrete possibilities involving the target word (e.g., 'Do you have a *car*?', 'Have you ever been in a *boat*?').

Responses were scored on a 0-3 scale for each memory produced, according to the specificity in time and place of the memory recalled. Scores were given for responses with and without cueing. A score of 3 was given for a memory with autobiographical involvement specifically limited to one time and place and rich in detail (e.g., 'When my eldest son was born I went to the village phone box to ring the hospital, then I rode through the village on my bike singing it's a *boy*!'). A score of 2 was given for a personal memory that had some specificity, but was not limited to one specific time and place (e.g., 'Handing out *stars* to boy scouts', 'Seeing the *flag* on top of church as a boy'). A score of 1 was given for a vague memory with no clear personal involvement (e.g., 'Looking at *stars* sometimes to judge weather'). A score of 0 was given for no response or a generic response (e.g., 'birds fly'). Total scores of 0–30, with and without cueing, were thereby obtained. Subjects were asked to estimate when any episode scoring 2 or 3 occurred. Dating by year, or personal age at the time of episode were permitted and allowed calculation of the age of episode.

The following day, without warning, subjects were retested. Each cue word was presented again and subjects were required to produce the previous day's memory. Responses were scored in the same 0–3 scale. Subjects were given 2 min to respond. If they failed to regain their day 1 score after 2 min, they were cued with key words from their day 1 memories (e.g., 'the day your *boy* was born') and were given a further 2 min to respond. Subjects were again asked to date the memories.

RESULTS

Clinical details

Principal details of all 5 patients are summarized in Table 1. For brevity, only Case 1 will be described in detail.

Case 1. E.S., a 58-yr-old council worker was in excellent general health with no past history of vascular disease, migraine or psychiatric disorder. During the morning of August 19, 1985, he went shopping with his wife and behaved normally. At 13.00 h he came into his house from the garden saying 'I don't know what has happened'. He was clearly amnesic and asked repetitively why he was not at work, what day it was, and what they had been doing. After seeing his general practitioner he was brought to the Radcliffe Infirmary at 15.00 h. On arrival he was profoundly amnesic. He was grossly disorientated in time. One indication of the severity of his anterograde amnesia was that when his wife left after being with him for the first hour of the interview he was unable to recall that she had been there. Although able to name 59 of 100 famous faces he frequently stopped during the test to ask what he was supposed to be doing, why he was at the hospital and where his wife was. When he was reexposed a few minutes later to 20 of the same set of faces plus 20 new faces his ability to pick out those he had seen previously was at the chance level.

Informal testing indicated a retrograde amnesia of between 3–6 months, with no clearly defined cut-off. He had no memory of his brother's death a few months previously and had forgotten visiting his brother-in-law in hospital 1 wk before. He had relatively good recollection of earlier events including his change of job following redundancy 2 yrs before. He could give accurate general information about his life. For example, he was able to recall that his wife was on regular home dialysis for renal disease and gave an accurate account of the procedure and its attendant problems.

He answered questions quietly and with deliberation. He was obviously bemused but otherwise showed little emotion. He appeared surprised and disturbed to hear that his brother had died, and wanted to hear further details of his brother-in-law's illness, but his reactions were muted and undemonstrative. In the Crovitz test his very limited account of a journey (prompted by the word 'train') lacked emotional vividness as well as factual detail. His recollections (which later proved to be dated prior to the dense retrograde amnesia) were curiously empty and lacking in colour, as if reduced to the bare bones of the memory. Apart from his profound amnesia there were no clinical abnormalities: speech was normal, reasoning was unimpaired and neurological examination was unremarkable.

By 20.00 (7 h postonset) his anterograde amnesia was showing signs of improvement and the retrograde amnesia had shrunk to a few days' duration. The following day he had virtually returned to normal. He proved to be an amiable, self-possessed man with an above-average knowledge of

TABLE 1 CLINICAL DETAILS OF 5 CASES EXAMINED DURING TGA

Case	*Age/ sex*	*Occupation*	*Past history*	*Length of attack*	*Informal estimate of retrograde amnesia*	*Permanent retrograde amnesia*	*Neurological signs*	*EEG*
1 (E.S.)	58 M	Manual worker	—	7 h	6–12 mos	½ h	Nil	N.D.
2 (L.V.)	67 M	Telephonist	Affective illness 1975	8 h	30–40 yrs	2 h	Nil	Normal (shortly after attack)
3 (W.D.)	61 M	Teacher	TGA 1979	7 h	A few hours	½ h	Nil	Normal
4 (L.G.)	49 M	Farmer	—	4 h	6–12 mos	1 h	Nil	N.D.
5 (V.E.)	73 F	Retired	—	10 h	1–2 yrs	2 h	Nil	N.D.

N.D. = not done.

public affairs. He had no memory of having done the Crovitz test but when given the target words produced many of the same memories, with strikingly increased colour and detail: the journey previously evoked by 'train' was recounted with obvious enjoyment and conviction.

Cases 2 to 5 resembled Case 1 in many respects, as shown in Table 1.

Previous medical history. The only patient with a psychiatric history was Case 2 who at the time of his attack was psychiatrically stable on lithium treatment following an affective illness 10 yrs previously. One patient (Case 3) had had a typical episode of TGA 6 yrs before.

Onset and duration of attack. None of the attacks was precipitated by acute psychological or physical stress. The onset of symptoms was always abrupt and was preceded by apparently normal behaviour. Four of the 5 patients were under close scrutiny, by family members, from the moment of onset. The first complaint was usually of vague distress, as in Case 1, but Case 3 said 'I think I am losing my memory'. Repetitive questioning was always an early feature of the attacks, with questions related to recent events. Case 5, who had been riding, kept asking 'Is Nellie (the horse) all right?' and 'I didn't have a fall, did I?'. Others asked questions such as 'What day/time is it?', 'What am I doing here?'. A witness noted that Case 4 would use identical phrases in each round of questions. The time of onset was known accurately in all cases. The length of attack was taken to be from the moment of onset to the moment when new memories were first formed, that is, from the subject's first recollection postattack. The duration of the attacks varied from 4–10 h.

Informal assessment of retrograde amnesia. General facts about personal life were often retained despite dense amnesia for remote public events. For example, names and personal details could be given for close family members. Amnesia was always dense for the day of the attack but the duration of dense retrograde amnesia, judged by questioning about recent personal and news events, ranged from about 40 yrs (in Case 2) to a few hours (in Case 3; *see* Table 1). There was never a clear cut-off point in the retrograde deficit nor was there selectivity between events of varying personal significance. There seemed to be a strong subjective sense of the type of information which the patients themselves expected to be able to recall. They often responded with the confident assumption that the answer to a question would be easily forthcoming, and then expressed frustration when an unexpected void was encountered, as if a familiar drawer had been opened and inexplicably found to be empty. In addition to total amnesia for the attack, all subjects had a permanent retrograde gap (for events prior to the onset) of between 30 min and 2 h.

Personality and behaviour. There was no evidence of confusion or clouding of consciousness, and rapport was good. All patients retained a sense of personal identity. No patient was indifferent, histrionic, or had features suggestive of a hysterical state. Patients seemed uniformly subdued and bewildered. A notable feature in all patients, as in Case 1, was a lack of spontaneity. Facts about personal life such as descriptions of holidays, or cued anecdotes in the Crovitz test, were recounted hesitantly and with detachment. As exemplified by Case 1, responses the following day were both more informative and more animated.

Language. All patients had normal aural comprehension, spontaneous language, confrontation naming, reading and writing. Picture description showed good syntax, vocabulary and understanding. Other normal results were the Boston naming test and tests of comprehension of complex ideational material, body part identification and commands from the BDAE (3 patients). Verbal fluency was normal in 4 patients, despite numerous perseverative responses.

Cognition. Reading was unimpaired. Attempts were made to deduce answers when memory failed, for instance by using clues in the famous faces test. The 3 patients given the 'Twenty questions' test (Cases 1, 2, 4) were able to apply complex hypotheses in a logical and systematic fashion. Constraint-seeking questions asked over 3 trials totalled 10, 12 and 15 respectively (normal controls 12 ± 2). Unlike patients with Korsakoff's syndrome, pseudoconstraining questions (*see* Methods) were rarely used (Butters, 1985).

Visuospatial function. All patients performed good, well organized copies of simple geometric shapes and of the Rey–Osterrieth complex figure. There was no evidence of spatial neglect or inattention.

Physical state. Cases 2 and 4 complained of abnormal sensations in the head. This was reported by Case 2 in a highly stereotyped and perseverative way: 'By the way, let me tell you, there is a slight pressure on top of my head.' No other physical symptoms were reported. Neurological examination was always normal and there was nothing to suggest cerebrovascular, cardiac or epileptic phenomena.

Investigations. A normal EEG was obtained during the attack in Case 3 and within hours of the attack in Case 2. All patients had normal CT scans.

Anterograde memory testing

The results of the formal anterograde memory tests, during and serially after the episode of TGA are shown in Table 2.

Immediate (short-term) memory. All subjects had forward digit spans within the normal range (6 ± 1). The backward digit span was mildly reduced in 2 subjects (3, 3, 4, 4, 5; normal controls 5 ± 1) and in all subjects it increased postattack by one digit. The Corsi block tapping span fell within the normal range (5 ± 1) during TGA, but increased in 2 subjects postattack, by one block.

Verbal memory. During TGA all subjects had a profound verbal learning deficit which improved only gradually postattack. Immediate recall of prose material was especially impaired (mean score 3.0; normal controls 10.8 ± 3.1), and usually consisted of the last few story items. After a delay of approximately 30 min there was no recall of material, even after prompting (normal controls 8.5 ± 3.0). Likewise, paired associate learning (PALT) was severely impaired with a mean score of 5.0 (normal controls 14.5 ± 3.3). No subject learned any 'hard pairs' over the 3 trials. After a delay of 30 min occasional 'easy pairs' were recalled.

The results of the drilled word list learning test are shown in fig. 1. Subjects were able to learn the six-word list to criterion quite normally, after 3, 3, 4, 5 and 6 trials respectively (normal controls 4.2 ± 1.9). Recall after 60 s (nondistracted) was 100% in all cases. However, following distraction for 3 or 10 min, no subject retained more than 50% of the material (normal controls retained virtually 100% throughout). Subsequently, the TGA subjects performed normally when tested at 6 months postattack when an eight-word list was used.

Nonverbal memory. Nonverbal memory was universally very poor during TGA. Although able to perform very good copies of the Rey-Osterrieth complex figure (mean score 29.6; normal controls 28.1 ± 4.4), after a delay of approximately 40

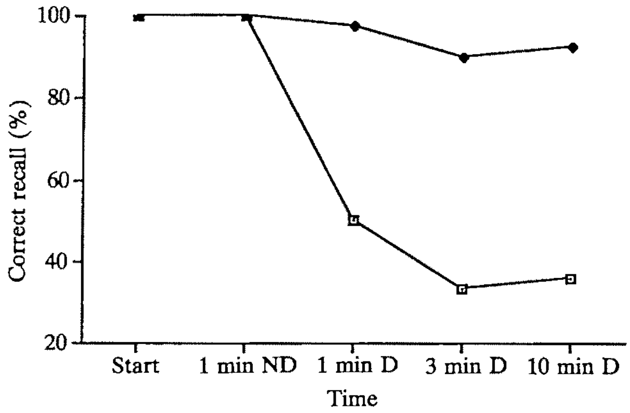

FIG. 1. Drilled word list learning test. Comparison of performance during and at 6 months post-TGA showing the mean percentage recall for the subject group after 1 min of nondistraction (ND), then after a further 1, 3, and 10 min of distraction (D) starting from a criterion of 3 correct trials. During (open squares); after (filled diamonds).

TABLE 2. RESULTS OF MEMORY TESTING DURING AND AFTER TGA

	Verbal memory							*Nonverbal memory*				*WAIS*		
	Digit span		*Paragraph*		*PALT*			*Corsi blocks*		*Rey-Osterrieth*				
	Forwards	*Reverse*	*Immediate*	*Delayed*	*Immediate*	*Delayed*	*Cd score*	*Span*	*Supra-span + 2 trials*	*Copy*	*Delay*	*Verbal*	*Performance*	*Full scale*
Case 1														
During	5	3	4.5	0	5.0	3	3.0	5	>20	27	0			
24 h	—	—	10.0	2.25	8.0	2	4.25	5	14	32	17			
1 wk	6	4	12.75	9.0	12.0	5	14.0	—	10	—				
6 mos	6	4	9.25	8.0	9.5	7	15.0	6	8	30.5	22.5	113	116	111
Case 2														
During	6	5	2.25	0	1.5	2	2.0	5	>20	30	0			
24 h	—	—	5.0	1.0	11.5	5	6.0	5	>20	—				
1 wk	6	6	14.0	9.75	8.5	2	11.75	—	12	32	19.5			
1 mo	—	—	10.75	7.25	12.5	6	13.25	—	—	—	—			
6 mos	6	6	9.0	6.75	10.0	6	12.75	6	7	34	17	114	113	114
Case 3														
During	5	4	3.25	0	6.5	6	6.0	5	>20	24	0			
24 h	5	5	6.0	4.0	8.0	6	10.0	5	12	20	7			
1 mo	—	—	9.5	4.25	10.0	4	8.25	—	—	34	13			
6 mos	6	5	13.0	10	14.5	9	19.0	5	5	31	10.5	132	117	127
Case 4														
During	6	3	3.0	0	7.0	3	3	5	>20	32	0			
24 h	—	—	7.5	5.0	8.0	4	9	5	>20	31	7			
1 wk	—	—	9.25	6.0	15.5	7	13	5	10	31	10			
1 mo	6	4	11.25	8.0	11.5	7	15	—	—	—	—			
6 mos	6	4	9.5	6.0	18.0	9	15	4	10	26	12.5	112	110	112
Case 5														
During	6	4	3.0	0	5.0	3	3.0	6	>20	—	—			
24 h	—	—	13.5	8.25	12	9	17.25	6	>20	35	9.5			
1 wk	—	—	13.5	11.5	16.5	8	19.5	6	5	31	15.0			
1 mo	7	5	—	—	15.5	9	—	6	5	—	—			
6 mos	6	5	12.75	10.25	18.5	9	19.25	5	4	32	17.5	122	131	127
Controls														
Mean	6	5	10.8	8.5	14.5	8.4	17.0	5	8.2	28.1	13.2			
SD	1	1	3.1	3.0	3.3	1.6	4.0	1	4.0	4.4	5.7			

PALT = paired associate learning test
Cd score = sum of delayed paragraph and delayed PALT scores

min no elements were produced by any subject (normal controls 13.2±5.7). Likewise, despite adequate immediate spatial memory, as demonstrated by a normal Corsi block tapping span, patients were unable to learn a sequence of two above span, even after 20 trials (normal controls 8.2±4 trials to criterion).

Two patients were given the spatial memory test of Smith and Milner (1981). After 4 min, Case 2 recalled no objects and Case 3 only 2 objects (normals 8.5±1.8 items). Object location was also extremely poor. Neither subject could recall the test, even when given the test items. Their object replacement was entirely random and bore no relationship to the original positions. The mean object displacement scores were 27.2 cm and 21.1 cm during TGA. When repeated at 6 months post-TGA both fell well within the normal range at 4.3 and 4.9 cm (normal controls 7.9±3.7 cm).

Recovery of anterograde learning. At 24 h all subjects felt that they had returned to 'normal', a view substantiated by their family and casual observers. However, formal tests revealed a persisting and substantial verbal and nonverbal memory defect. The verbal deficit was most marked on delayed paragraph and paired associate recall. Fig. 2 shows the recovery of Cd (combined delayed paragraph and PALT) scores. All subjects had improved at 24 h after the attack but 4 of the 5 were still substantially impaired at this stage. Further improvement continued between 24 h and 1 wk in 4 subjects. All improved to a lesser degree between 1 wk and 6 months. The most rapid improvement occurred in the youngest subject (Case 5, aged 49 yrs). At 6 months all except Case 3 fell within the normal range (17.0±4.0).

Sequential nonverbal memory test scores are shown in fig. 3. All subjects remained impaired at 24 h on the Corsi supraspan learning test and 2 subjects improved markedly between 1 wk and 6 months after the attack. Similarly, on delayed reproduction of the Rey-Osterrieth complex figure, although there was

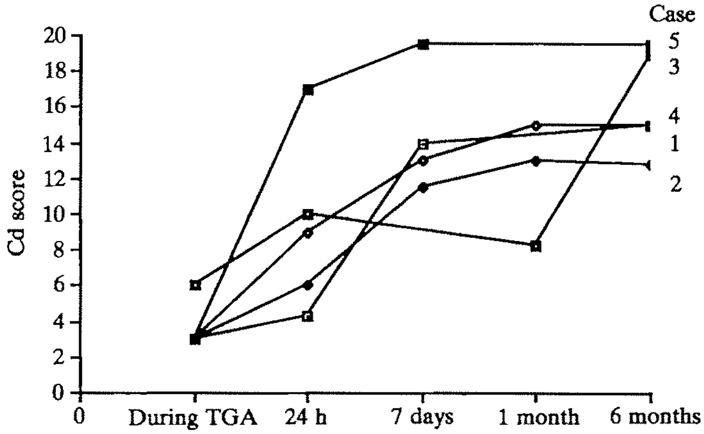

FIG. 2. Recovery of verbal memory post-TGA. The combined delayed paragraph and paired associate learning (Cd) score is shown for each case during and sequentially after TGA.

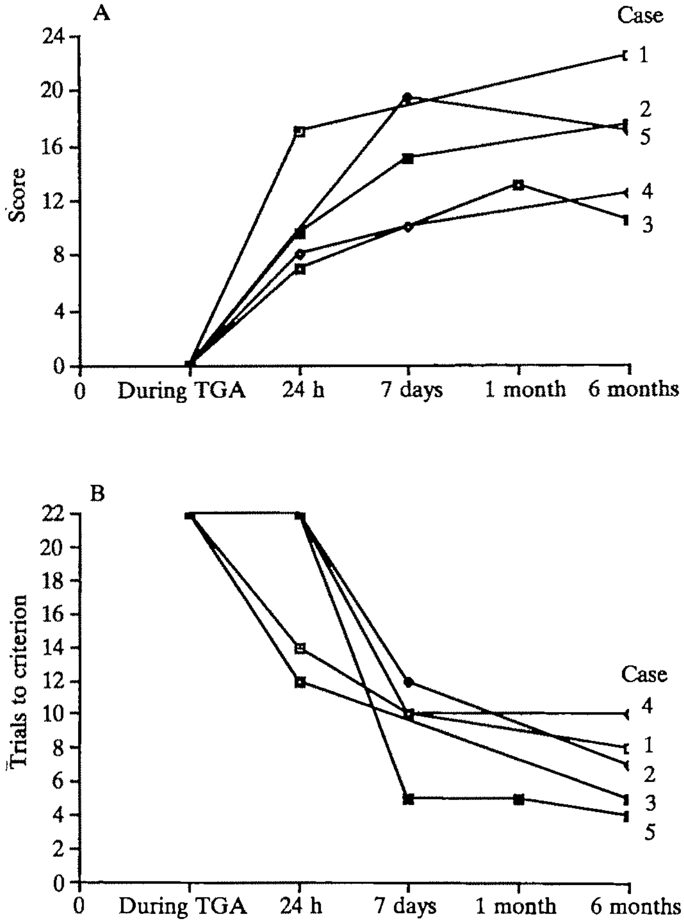

FIG. 3. Recovery of nonverbal memory post-TGA. The delayed Rey-Osterrieth figure score (A) and the number of trials to learn a supraspan (+2) Corsi block tapping sequence (B) are shown for each case during and sequentially after TGA.

improvement at 24 h, 3 of the 4 tested were still clearly defective. Of the 3 subjects tested at 1 wk, 2 remained impaired but improved further when seen at 6 months. At 6 months all subjects fell within the normal range (13.2±5.7).

Remote memory testing

Famous faces test. There was considerable variation in scores between the 5 subjects tested during TGA. However, statistical analysis showed a significant overall improvement in postattack scores, with evidence of a temporal gradient. Fig. 4 compares the scores for individual subjects during the attack with those of the normal controls. The decades analysed depended on the age of the subject (*see* Methods). Compared with the normal controls, subjects showed wide variation; only Cases 1 and 4 could be considered 'normal' for all decades. Cases

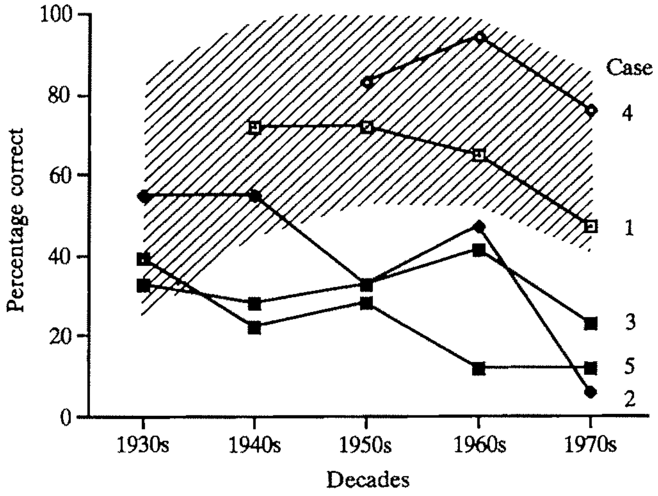

FIG. 4. Naming of famous faces during TGA. The score per decade for each case is shown. The decades included depend on the age of the patient. The normal range (indicated by the hatched area) was taken as the mean ±2 SD for 50 matched controls.

2, 3, and 5 had an extensive deficit; of these, Case 2 was 'normal' only for test items from the 1940s, and Cases 3 and 5 were impaired on all decades.

Comparison of the scores for each subject for each decade during TGA with scores for the same decades 6 months later showed a highly significant improvement (Wilcoxon signed-rank test, $P < 0.001$). Fig. 5 shows the mean score per decade during TGA as a percentage of the corresponding mean score postattack. Improvement was most marked for recent decades. The ratio of the scores for the earliest decade and the most recent decade was used as an index of temporal gradient. The gradient was significantly higher during TGA than on subsequent testing (Wilcoxon signed-rank test, $P < 0.05$).

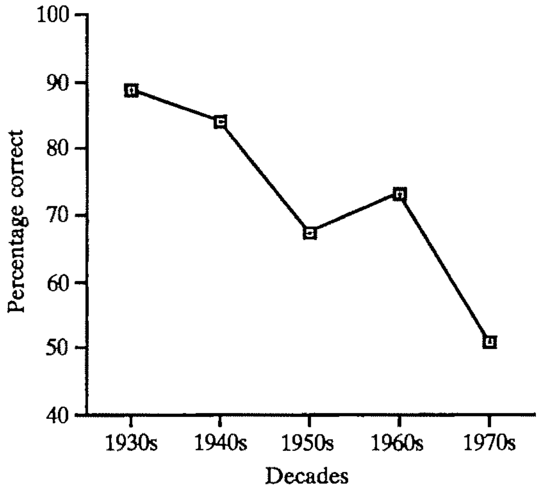

FIG. 5. Comparison of famous face naming during and after TGA. The mean score of the subject group per decade during TGA is shown as a percentage of the corresponding mean score at 6 months post-TGA.

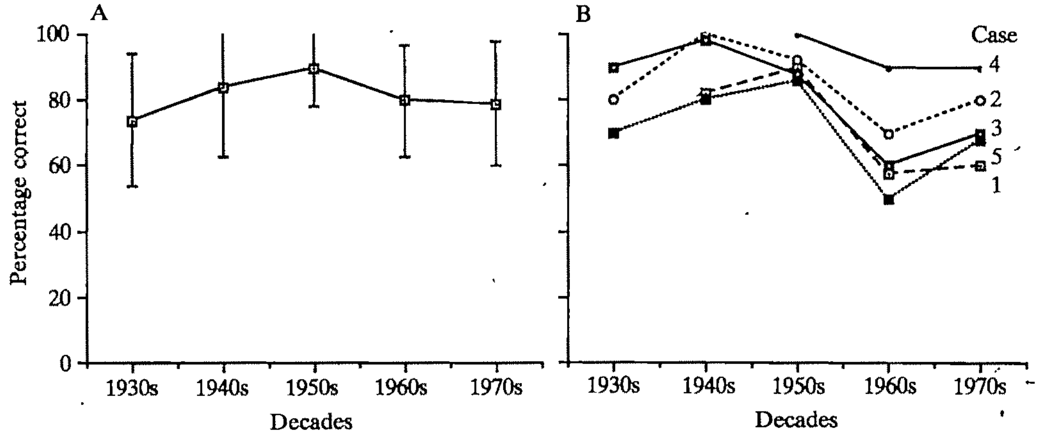

FIG. 6. Recognition of famous events during TGA. The mean score (±2 SD) per decade of the 50 matched normal controls (A) and the scores of the individual TGA cases (B) are shown. The decades included depend on the age of the subject.

Famous events test. Recognition of famous events was normal during TGA. Fig. 6 compares the test scores per decade for the 5 subjects with those of the normal controls. As with the famous faces test, only events that occurred after each subject had reached the age of 15 yrs were included in the analysis. All subjects were within the normal range. Comparison of the scores for individual subjects during and 6 months postattack revealed no significant difference (Wilcoxon signed-rank test, $P > 0.05$). Fig. 7 shows the mean scores during TGA for each decade as a percentage of the corresponding mean postattack scores. When the ratio of the scores for the earliest decade and the most recent decade were compared, there was no evidence of a significant temporal gradient effect (Wilcoxon signed-rank test, $P > 0.05$).

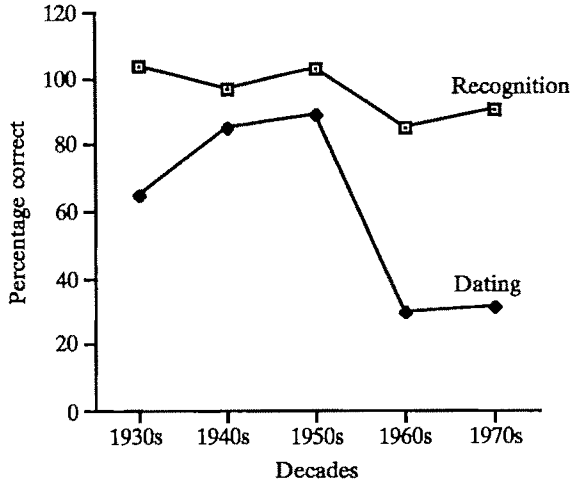

FIG. 7. Comparison of famous events recognition and dating, during and after TGA. The mean score of the patient group, per decade, during TGA is shown as a percentage of the corresponding mean score at 6 months post-TGA.

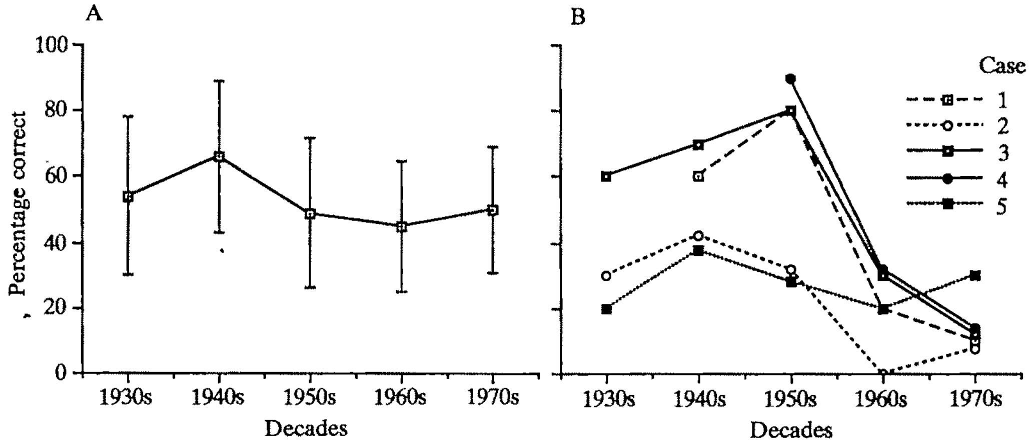

FIG. 8. Dating of famous events during TGA. Showing the mean scores (±2 SD) per decade of the 50 matched normal controls (A) and the scores of the individual TGA cases (B). The decades included depend on the age of the subject.

As the test consisted of 50 real events and 50 fictitious events it was theoretically possible to achieve a high score by guessing all items to be true (i.e., confabulating). A d′ score was therefore calculated (the total true positive responses minus the false positive responses) to allow for guessing. False positive responses ranged from 6% to 10% during TGA, a rate that was not significantly greater than among controls (8±2%; $\chi^2 = 0.12$, $P > 0.05$). Thus the d′ scores approximated very closely to the total true positive scores, giving no evidence of confabulation during TGA.

In contrast to normal event recognition, dating of events was impaired during TGA. Furthermore, there was evidence of a temporal gradient. Fig. 8 compares the scores for individual subjects, per decade, with those of the normal controls. All cases showed impaired dating of events from the 1960s and 1970s. Two (Cases 2, 5) showed impairment across all decades. Matched-pair analysis of scores during and 6 months post-TGA revealed a highly significant difference (Wilcoxon signed-rank test, $P < 0.001$). Fig. 7 shows the mean scores during TGA for each decade, as a percentage of the corresponding mean postattack scores. There was a significant temporal gradient effect when comparing the ratio of the earliest and the most recent decade scores (Wilcoxon signed-rank test, $P < 0.01$).

Personal remote memory (modified Crovitz) test. The cued personal autobiography test was performed on 3 subjects during TGA (Cases 1, 2, 4). It was repeated at 24 h and 6 months using the same word list. Normal controls find this test extremely easy; they are usually able to produce specific memories rich in detail (mean scores: 28.3±1.9 uncued, 29.2±1.4 cued) which are then consistently reproduced and dated 24 h later (day 1-day 2 dating correlation in controls, r = 0.98). Subjects were unable to recall having done the task during TGA, and were therefore cued to produce the same episodes as during the attack so that these could be redated. Corroboration of episode dates was obtained from spouses. The pattern of results differed between the 3 subjects, although the age distribution of the memories recalled was uniformly abnormal.

Case 1 found the test difficult. He produced memories which were temporally specific, but lacking in detail (scores: 19 uncued, 25 cued), with a mean age of 13.8 yrs. When retested at 24 h and subsequently at 6 months he obtained normal cued scores (30 and 29) and gave the same memories with mean ages of 8.4 and 9.5 yrs. Thus it would appear that during TGA he consistently overestimated the age of the personal memories.

Case 2 produced a reasonable number of specific episodes only after cueing (scores: 16 uncued, 27 cued), with a mean age of 3.7 yrs. When retested at 24 h and 6 months the same memories were given a mean age of 11.5 yrs and 11.8 yrs, respectively. His wife verified 9 of the 10 episodes and she gave them a mean age of 10.7 yrs. Thus it would appear, that during the attack he systematically underestimated the age of personal memories.

Case 4 performed this test more normally during TGA. Although his uncued score was low at 25, with cueing he produced highly specific memories (score 30) rich in detail, with a mean age of 30.7 yrs. The same memories were given estimated mean dates of 30.4 and 28.8 yrs when retested at 24 h and 6 months respectively.

Fig. 9 shows the age distribution of the memories produced by the 3 subjects (using the date estimates given at 24 h postattack) compared with the age distribution of memories produced by the normal controls. Approximately 25% of the total number of memories produced by normal controls come from the most recent 5 yr period and 16% are less than 1 yr old. During TGA only 4% of the total were from the most recent 5 yr era and all were older than 1 yr.

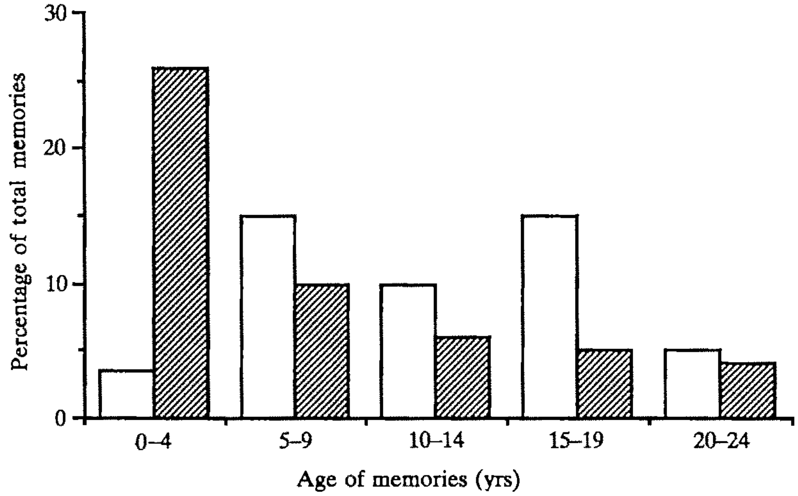

Fig. 9. Modified Crovitz test. Comparison of the age distribution of the total number of memories produced by 3 subjects during TGA (unhatched columns) with those produced by 50 matched normal controls (hatched columns).

DISCUSSION

Our observations of 5 patients during and following TGA relate to several issues which will be considered in turn. First, we have been able to confirm that TGA is purely an amnesic syndrome and we have extended previous observations on the nature of the anterograde amnesia. There is preservation of immediate (short-term) memory but longer-term memory for verbal and nonverbal material is profoundly disrupted in all cases. Secondly, we have quantified the extent and pattern of retrograde amnesia. In contrast with the deficit in learning new material, the severity of retrograde amnesia appears more variable. It shows a temporal gradient with recent material being less well retrieved and there is evidence of a defect in dating past memories. Despite the anterograde and retrograde amnesia there is preserved awareness of which memories ought to be readily recalled, so-called 'metamemory' (Hirst, 1982; Shimamura and Squire, 1986). Moreover, there is no apparent loss of the material required to give meaning and continuity to sensory experience, termed 'semantic memory' (Tulving, 1983). Thirdly, we have considered the pathophysiology of the amnesia and the relevance of the findings in TGA to models of the amnesic syndrome. A fourth area of interest is the pattern of recovery of memory function following the attack, which appears to be protracted. Finally, our observations have relevance to questions about the aetiology of TGA.

The nature of the anterograde amnesia

The amnesic syndrome appeared to be pure. Descriptions of 'confusion' during TGA are misleading. Our patients attempted to orientate by using environmental cues, remained capable of manipulating complex and abstract information, and reasoned coherently. All aspects of language and visuospatial function tested were normal. The single most consistent finding was of severe anterograde amnesia which affected both verbal and nonverbal learning capacity. Despite this deficit immediate (short-term) recall was normal, as judged by both forward digit and block-tapping spans. The latter finding accords with previous observations during TGA (Wilson *et al.*, 1980; Regard and Landis, 1984). The dissociation between immediate (short-term) and longer-term memory is also characteristic of permanent amnesic syndromes, whether due to diencephalic damage, as in Korsakoff's disease (Baddeley and Warrington, 1970) or bitemporal damage, as exemplified by case H.M. (Milner *et al.*, 1968). Subjects were able to learn a shortened (six-word) list to criterion normally. They retained the list when able to rehearse; after distraction forgetting was rapid and within minutes was absolute. Prose recall was severely impaired, as was paired associate word learning. After a delay, recall was negligible, even with prompting. There was also severe anterograde amnesia for nonverbal material. Two tests which are considered relatively selective for right hemisphere memory function—learning a supraspan block-tapping sequence

(De Renzi *et al.*, 1977) and incidental spatial recall (Smith and Milner, 1981)—showed profound impairment.

It is possible that the apparent uniformity in the severity of anterograde amnesia resulted from a 'floor effect'. More simple tests of memory might have demonstrated differences in the severity of anterograde learning. However, such tests could scarcely alter the conclusion that in TGA there is a universal and gross impairment in the ability to learn both verbal and spatial material.

Extent and pattern of retrograde amnesia

The interpretation of remote memory tests is difficult and deserves consideration. In patients with permanent amnesia, the extent of remote memory loss must be judged with reference to normal controls. This poses major problems given the great interindividual variation in knowledge of public material. In addition, nonrecognition or recall of a face or an event could result either from original ignorance or from amnesia and there is no way of verifying the content of remote memory. Our methods capitalized on the possibility of testing the same subjects during and after recovery from an amnesic episode.

Famous faces tests have been widely used to assess retrograde amnesia but they pose serious methodological problems. Faces remain famous for variable lengths of time. The date at which a famous face has been registered can never be precisely known and the selection of date-specific faces is extremely difficult. Those selected from earlier decades may have greater salience than more recent faces, thus creating an artificial gradient when memory fails. The faces that we used were not ideal and some undoubtedly spanned more than a single decade. The famous events test was designed to overcome some of the difficulties inherent in famous faces tests, to extend testing to nonvisual material which could be precisely dated, and to monitor false recognition or confabulation objectively. It should be noted that the test was based on recognition, rather than recall. The results are therefore not directly comparable to the famous faces test. Tests of personal memory should, in theory, overcome the methodological problems of public events tests (nonequivalence of test stimuli, reexposure to old events/faces) since the effects of prior rehearsal are equated across the test. However, the quantitative assessment of autobiographical memory in permanent amnesia depends on independent corroboration of the subject's biography. Again, the reversibility of TGA permitted the extent and pattern of autobiographical retrograde memory loss to be assessed in comparison with post-attack test results. The Crovitz test was particularly useful, since standard cues could be used to access the same personal memories both during and subsequent to the attack.

Taken together, the three quantitative tests and the informal assessments confirmed that all patients had retrograde amnesia, but by comparison with the universally severe anterograde deficit, the retrograde deficit appeared more variable in extent. Moreover, there was a characteristic temporal gradient with sparing of more distant memories. All 5 cases showed retrograde amnesia for public events as judged from famous face identification and famous event dating. The lack of impairment in famous event recognition might merely have reflected the less demanding nature of the recognition task. Another possibility is that recognition of such events draws on a store of general, context-free or semantic knowledge, whereas dating requires memory of a more specific contextual or episodic nature. The absence of false positive responses in the famous events test confirmed the clinical observation that confabulation was not a feature of the amnesia. The 3 subjects given a test of autobiographical memory all had a degree of retrograde amnesia, as indicated by reduced scores in the uncued paradigm and by their inaccurate dating of memories. They also contrasted with normal controls in their failure to produce memories from the most recent 5 yrs. A normal recency effect for remote autobiographical memories has been consistently demonstrated by all workers in this field (Crovitz and Schiffman, 1974; Zola-Morgan *et al.*, 1983; Sagar *et al.*, 1988). We were also struck by the qualitative differences in the memories produced during TGA, which although temporally specific were often lacking in the richness and detail with which the same memories were related postattack. In future studies it would be interesting to pursue autobiographical memory in more detail and in particular to temporally constrain (to specific life periods) responses during TGA.

Pathophysiology of the amnesia and theoretical implications

Models of human memory and amnesia have been based very largely on studies of patients with permanent memory loss. While some investigators seek to explain anterograde and retrograde amnesia in terms of a storage or consolidation defect (Milner, 1966; Cohen and Squire, 1981; Squire, 1986), others favour a general retrieval deficit (Warrington and Weiskrantz, 1970; Weiskrantz, 1985). Central to all such theories is their explanation of the phenomenon of retrograde amnesia, particularly since different patterns of remote memory loss have been associated with specific aetiologies. Patients with bitemporal damage, such as the celebrated case H.M. (Milner *et al.*, 1968; Marslen-Wilson and Teuber, 1975; Corkin, 1984) or patients post-ECT (Squire *et al.*, 1975; Cohen and Squire, 1981; Squire, 1982) have a temporally limited retrograde amnesia, ranging from a few months to a few years. By contrast, patients with alcoholic Korsakoff's disease have a temporally extensive retrograde loss spanning many decades. All investigators agree that Korsakoff patients have an extensive remote memory loss but there has been disagreement over the temporal profile (Sanders and Warrington, 1971; Weiskrantz, 1985). The balance of evidence favours a temporally graded loss which appears to reflect a true sparing of distant memories rather than an artefact due to test construction (Marslen-Wilson and Teuber, 1975; Albert *et al.*, 1979; Selzer and Benson, 1974; Meudell *et al.*, 1980; Cohen and Squire, 1981; Butters, 1985).

The diversity in retrograde amnesia has been difficult to accommodate to either the storage-consolidation or the retrieval hypotheses. Hence, it has been argued that the extensive temporally graded memory loss in Korsakoff's syndrome must be either (1) secondary to a progressive defect in the encoding of new memories, during the 20 or so yrs of alcohol abuse that precede the onset of the amnesic syndrome (Squire and Cohen, 1982; Butters and Albert, 1982), or (2) due to additional cognitive deficits unique to Korsakoff's syndrome (Squire, 1986). However, experimental group studies of nonamnesic alcoholics and detailed single case studies in Korsakoff's syndrome have not provided strong support for this hypothesis (*see* Butters, 1984, 1985). The elucidation of the extent and pattern of remote memory deficit in conditions other than Korsakoff's syndrome is clearly important. We have established that during TGA there is a temporally graded and sometimes extensive retrograde amnesia, which is reversible postattack. This deficit cannot be explained on the basis of a disturbance of encoding or consolidation. We suggest that it must be due to a temporary retrieval deficit. Our findings would support the idea that the age of memories is an important property which under certain circumstances is relevant to their retrieval, as originally suggested by Ribot (1882). It may be that older personal or episodic memories acquire the properties attributed to semantic memory and are thus rendered more resistant to retrieval deficits such as in TGA.

In looking for a mechanism underlying the retrieval deficit we considered the possibility of a specific defect in dating or sequencing past events. As already noted, other authors have commented upon defective chronological judgement during and immediately after TGA (Caffarra *et al.*, 1981; Regard and Landis, 1984; Gallassi *et al.*, 1986). We observed difficulty in dating past memories during informal interview and on formal testing. All subjects were able to distinguish real from fictitious events but were severely impaired when dating historical events. Two of the 3 patients given the Crovitz test demonstrated a similar difficulty in estimating the age of personal memories. It is at present unclear whether temporal disorganization is merely an especially sensitive indicator of a general disorder of retrieval or whether a primary defect in memory sequencing could radically impair other aspects of retrieval. Studies of patients with Alzheimer's disease and Parkinson's disease support the latter hypothesis since the ability to date events and the ability to recall or recognize them may be dissociable (Sagar *et al.*, 1988).

The relatively stereotyped pattern of neuropsychological deficit might be expected to suggest a unifying pathogenetic hypothesis. In other words, does a 'core deficit' underlie TGA? The unimpaired immediate memory shows that material can be registered normally. The permanent amnesic gap indicates a defect in the process required for the acquisition of memory and the extensive, but reversible retrograde amnesia implies a retrieval deficit. One unifying possibility is that the transfer of data into and out of long-term storage from working memory is interrupted. The relationship between anterograde and retrograde amnesia is clearly important in this regard. These two features were always present during the attack, but whereas all patients appeared to have an equally profound anterograde deficit, the extent of the retrograde loss varied considerably. This finding is not easily reconciled with the view that a single cognitive deficit causes both anterograde and retrograde amnesia. Instead, the processes of encoding new and retrieving old memories, while functionally and even anatomically closely related, appear to be dissociable. Further studies are clearly required before definite conclusions can be reached. However, clinical studies of patients with permanent memory disorders have provided some support for this hypothesis by showing that anterograde and retrograde amnesia may occur independently of each other (Goldberg *et al.*, 1982; Kapur *et al.*, 1986; Shimamura and Squire, 1986).

Recovery following TGA

During the recovery phase there is a progressive return of distant memories followed by more recent ones. This pattern of 'shrinking retrograde amnesia' is similar to that described following closed head injury (Benson and Geschwind, 1967). Recovery of anterograde memory function after TGA appears superficially to be rapid with a subjective return to normality within 24 h. However, it is clear that subclinical impairment persists for some time. Vestiges of the memory deficits characteristic of the attack could be consistently detected 24 h postattack. Further improvement occurred between 7 days and 1 month in 4 of the 5 subjects tested and performance in 1 subject clearly improved even further at 6 months postattack. Nonverbal memory improved more rapidly than verbal memory. Although our patients' memory functions improved to within the normal range, it remains possible that their performance post-TGA was still below their pre-TGA level. There is some evidence that verbal memory may be permanently impaired after TGA (Mazzucchi *et al.*, 1980). One of us (J.H.) is currently conducting a larger controlled follow-up study to clarify this point.

Following recovery from TGA, subjects are left with a dense amnesic gap for the duration of the attack. In addition, we have observed that there was a short permanent retrograde amnesia of between 30 min and 2 h, covering the period before the apparent onset of the attack. Recovery from TGA was gradual, without an apparent clear cut-off; although afterwards patients were usually able to recount their first impressions on 'coming to'. The onset, however, was always abrupt. Four of our patients' attacks were witnessed from the beginning and their behaviour appeared perfectly normal until the moment of onset. Fisher (1982) has previously reported permanent retrograde memory loss post-TGA and commented on its remarkably long duration as compared with that after closed head injury (Russell, 1971). This permanent loss of memory for events before TGA suggests that a provess of active remodelling or consolidation may occur, for some hours, during which time recently acquired memories are susceptible to permanent erasure.

The aetiology of TGA

Observations made on patients during episodes of TGA should contribute to the question of its validity as a distinct syndrome (Caplan, 1985). Our observations show considerable uniformity of clinical and neuropsychological features. The behavioural changes in our patients were similar. Subjects exhibited a pure amnesic syndrome and although the overall severity of the retrograde amnesia was variable, many of the properties of the amnesia itself were qualitatively similar. The pattern of recovery was a further unifying feature of the syndrome. Clinical uniformity suggests a shared pathophysiological mechanism, although not necessarily a single aetiology. The three most commonly advocated mechanisms are cerebral ischaemia, epilepsy, and hysteria. Fisher and Adams (1964) favoured epilepsy as the likely cause. In a review 20 yrs later, Fisher (1982) still considers that 'ischaemia of the cerebrovascular variety plays no part'. Confirmatory evidence, however, has been lacking, and the development of overt epilepsy is rare, as are significant EEG abnormalities (*see* Markowitsch, 1983; Caplan, 1985; Miller *et al.*, 1987). Our clinical data provides no support for an epileptic aetiology. Patients remained lucid without automatism and EEGs obtained during, or shortly after an attack were normal. The majority of subsequent authors have proposed a cerebrovascular aetiology (Heathfield *et al.*, 1973; Mathew and Meyer, 1974; Jensen and Olivarius, 1980; Shuping *et al.*, 1980; Logan and Sherman, 1983; Cattaino *et al.*, 1984), although supportive epidemiological evidence is lacking (Caplan, 1985; Hodges and Warlow, 1985; Kushner and Hauser, 1985; Hinge *et al.*, 1986).

The most cogent evidence against a psychiatric aetiology is the gradual improvement in memory function in the period after the amnesic attack, when patients denied any deficit. Premorbid features in psychogenic amnesia include personality disorder, a past history of hysterical phenomena, suicide attempts or alcoholism, as well as clearly identifiable precipitating stresses and potential gains (Sargent and Slater, 1941; Kennedy and Neville, 1957; Kopelman, 1987). These conditions were lacking in our patients. The nature of the memory loss in psychogenic amnesia has received surprisingly little attention. Merskey (1979) states that new material can be learned normally, and that responses and behaviour tend to be inconsistent; Kennedy and Neville (1957) and Merskey (1979) stress suggestibility and loss of personal identity. A sharp cut-off in retrograde amnesia may indicate a psychogenic mechanism (Schacter, 1986). The only case to have been studied in detail during an attack is that of Schacter *et al.* (1982); where responses in a version of the Crovitz test tended to be inconsistent in successive testing sessions, a relatively intact island of memories could be identified, and there was no temporal gradient in retrograde amnesia. Personal identity was lost while ability to learn new material was retained. These features contrast sharply with our observations of TGA.

In conclusion, we have presented evidence that during TGA there are characteristic neuropsychological abnormalities which closely parallel those found in the permanent amnesic syndrome. The anterograde amnesia appears to be pure, profound and global. The retrograde amnesia is variable in extent. Formal tests confirm a temporal gradient which is reversible and must therefore be a consequence of temporary retrieval deficit. Recovery of memory is slow and may continue for weeks.

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CHRONIC HYPERALGESIA AND SKIN WARMING CAUSED BY SENSITIZED C NOCICEPTORS

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SUMMARY

A patient suffering from an acquired painful syndrome, due to injury to primary somatic afferent units, was studied. Clinical features included chronic spontaneous burning pain in one hand, abnormal painful response to nonnoxious cutaneous stimuli, and deviation of temperature and dystrophic changes in symptomatic skin. Diagnostic stellate ganglion blocks did not improve spontaneous or stimulus-induced pains, and observation of sympathetic efferent neural activity and vasomotor effector responses revealed no abnormality, failing to support an autonomic contribution to the pathogenesis of the pains.

A quantitative psychophysical assessment documented exaggerated magnitude of pain in response to noxious stimuli in symptomatic skin, together with abnormal painful quality and prolongation of sensation induced by nonnoxious tactile or warm stimuli. Such mechanical and thermal hyperalgesia persisted during A fibre blocks, suggesting transmission by primary afferents with unmyelinated C fibres and implying sensitization of C polymodal nociceptors. Direct microneurographic recordings of single, identified C polymodal nociceptors from symptomatic skin confirmed the presence of units with pathologically enhanced receptor responses: lowered threshold and very prolonged afterdischarges. While bypassing skin receptors, strongly intraneural microstimulation in fascicles supplying symptomatic or control skin evoked equivalent magnitudes and temporal profiles of pain from both sides. Thus secondary CNS dysfunction need not be postulated to explain the painful syndrome.

Skin grafted onto the affected region partially recovered tactile and thermal sensation (but not pain) without expressing the painful syndrome. This supports the overall conclusion that in this patient A fibres are not involved as primary carriers of input decoded as pain.

Sensitization of C polymodal nociceptors is consistent with the features of hyperalgesia in this patient: pain evoked by nonnoxious stimuli, exaggerated pain magnitude, and abnormally prolonged aftersensation of pain. This is the first documentation of chronic sensitization of human C polymodal nociceptors as a symptom of disease. In the context of sensitized C nociceptors and in the absence of sympathetic vasoconstrictor deficit, the abnormally elevated temperature in symptomatic skin is interpreted as due to antidromic vasodilatation triggered by neurosecretion from hyperactive nociceptors.

This study calls for reexamination of concepts relating to hyperalgesia as a sequel of injury to the peripheral nervous system, and to reflex sympathetic dystrophy, and presents pathophysiological

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data on a particular variety of neuropathic painful syndrome featuring signs of vasomotor dysfunction.

INTRODUCTION

The chronic somatosensory aberration consequent upon injury to the nervous system in which even gentle touching, warming or cooling may cause pain, represents a source of disability and an area of scientific perplexity. This clinical phenomenon, classically termed hyperalgesia, was defined by Head as 'increased sensitiveness to pain or *hyperalgesia*' (Head, 1893, p. 128), and later was taken to mean lowered threshold for pain sensitivity and increased pain magnitude to suprathreshold stimuli. The concept has been recently subdivided into *allodynia*, i.e., 'pain due to a stimulus which does not normally provoke pain', and *hyperalgesia*, i.e., 'an increased response to a stimulus which is normally painful' (Lindblom *et al.*, 1986). For consistency with earlier experimental literature we chose the definition of hyperalgesia: lowered threshold for pain sensitivity and increased pain magnitude to suprathreshold stimuli.

As a short-lived event, hyperalgesia can be readily reproduced experimentally by mechanical, thermal or chemical challenge to human skin or cutaneous nerves. Pioneer investigators (Lewis, 1936*a*, 1942; Jung, 1941) largely explained it through sensitization of cutaneous nerve endings, long before this anomaly was recorded electrophysiologically in similarly challenged animals (Bessou and Perl, 1969; Beck *et al.*, 1974; Beitel and Dubner, 1976; Croze *et al.*, 1976; Kumazawa and Perl, 1977; Fitzgerald, 1979; Lynn, 1979; Lynn and Carpenter, 1982; Campbell and Meyer, 1983). Recently, sensitized C polymodal nociceptors have been directly demonstrated by microneurography in acute experimental hyperalgesia in human volunteers (Torebjörk and Hallin, 1977; Konietzny and Hensel, 1983; LaMotte *et al.*, 1984; Torebjörk *et al.*, 1984*a*).

While a reasonable pathophysiological explanation is available for experimental hyperalgesia, the issue becomes complicated for clinical hyperalgesia. First, these experimental hyperalgesias are acute, short-lived models, not necessarily equivalent to the clinically significant chronic hyperalgesias seen in the realm of neurological disease. Further, the latter may feature 'secondary hyperalgesia' characteristics thought to be due to reactive hyperexcitability in the central nervous system, determined by initial injury to primary afferents (Hardy *et al.*, 1952; Woolf, 1983; Raja *et al.*, 1984; Roberts, 1987). In this case, the afferents for the primary input ultimately decoded as inappropriately painful would not be nociceptors but low threshold fast conducting mechanoreceptor afferents. Indeed, reaction times for hyperalgesic pain response have been found short enough to be mediated by fast conducting primary afferents with A fibres (Lindblom and Verrillo, 1979; Fruhstorfer and Lindblom, 1984), and selective A fibre block through compression-ischaemia has been reported to cause early abolition of hyperalgesic response to nonnoxious stimuli (Wallin *et al.*, 1976; Ochoa, 1982; Meyer *et al.*, 1985, 1987).

On these grounds, a central disorder is often favoured to explain chronic hyperalgesia symptomatic of injury to the peripheral nervous system. The alternative concept of nociceptor sensitization, tacitly dismissed in those reports, is explicitly rejected by Wall, who peruses hyperalgesia to question the concept of somatosensory specificity (Wall, 1984).

Here we describe and discuss detailed investigation of one of several patients expressing the chronic hyperalgesic phenomenon in whom, on the basis of reaction times and A fibre blocks, the abnormal painful response to nonnoxious stimuli is mediated by units with C fibres, rather than by primary afferents with A fibres. Microneurography corroborated that C polymodal nociceptors had sensitized cutaneous endings exhibiting pathological responsiveness to low intensity stimuli. These abnormal nociceptor characteristics explain the abnormal painful quality and the prolonged after-sensation in response to nonnoxious stimuli, together with the exaggerated magnitude of pain in response to noxious stimuli. Intraneural microstimulation, used to compare pain evoked by excitation of nerve fibres supplying symptomatic and control skin, revealed no apparent abnormality in central processing of the inputs. Observations up to one year after partial skin graft added support to the overall concepts (1) that this patient's hyperalgesia is not mediated by primary low threshold mechanoreceptors, but (2) it is mediated by C nociceptors with abnormal receptor characteristics, and (3) that the CNS does not appreciably contribute to his hyperalgesia.

It is proposed that the documented sensitization of C polymodal nociceptors and the thermographically observed regional vasodilatation of the symptomatic skin are pathophysiologically related. The proposed link is spontaneous impulse initiation from sensitized receptor endings with axon reflex, antidromic vasodilatation caused by neurosecretion of active substances from C polymodal nociceptor endings. Whereas nociceptor sensitization in this patient is regarded as a direct consequence of exogenous physical injury, it is proposed that the primary abnormality in other patients may result from ectopic impulse activity at midaxon level in diseased nociceptor units. This activity would lead to orthodromic conduction evoking painful sensory experience, and antidromic conduction triggering neurosecretion (Ochoa, 1986; Ochoa *et al.*, 1987*a*). The latter would determine not only vasodilatation, but also nociceptor sensitization, thus establishing a selfperpetuating vicious circle (Lewis, 1936*b*; Jung, 1941; Chapman *et al.*, 1961; Fitzgerald, 1979; Ochoa, 1986).

By documenting sensitization of nociceptors in human disease, the present investigation calls for expansion of prevalent concepts of chronic pain and hyperalgesia from injury to the nervous system, in particular, the entity 'reflex sympathetic dystrophy'. It also challenges the basis for a 'challenge to specificity theory' (Wall, 1984). It is hoped this report may stimulate research efforts directed towards the control of neurogenic inflammation and its consequences.

CASE HISTORY

A 43-yr-old man noted onset of touch-induced pain in July 1984. After 5 days of sun exposure during a fishing trip, he developed a skin rash in upper limbs, worse on the dorsum of the right hand and index finger. The sunburn and skin rash resolved but the sore skin on the right hand persisted indefinitely. He had a 9-yr history of recurrent light-induced skin rash, known as polymorphous light eruption (Jansén and Karvonen, 1984; Kaidbey and Messenger, 1984), but had never developed persistent skin sensitivity before the 1984 exposure. Lightly touching the involved area of skin produced an intense sensation of burning pain, which markedly interfered with his capacity to perform custodial duties at work. Frequent or repetitive use of the right hand induced spontaneous ongoing burning pain. He learned the necessary manual skills with his left, nondominant, hand.

In addition to the presence of mechanical hyperalgesia, gentle heat stimulation, such as when exposing the hands to warm water, evoked severe pain in the right. In contrast, cooling improved the pains. For example, walking outdoors in very cold weather relieved ongoing pain, if present, and strikingly decreased or abolished mechanical hyperalgesia. With time, stimulus-induced pain became easier to provoke, and intensity and duration of pains became progressively worse. Family history was negative for similar dermatological or neurological complaints.

The patient was referred to our unit for neurological evaluation in September 1985 with a diagnosis of reflex sympathetic dystrophy. After obtaining informed consent, special tests were performed, the course of several of which was videotaped.

METHODS

Thermography

The thermal emission profiles of hands and forearms were tested on repeated occasions between September 1985 and 1987. Contact thermography was performed, using a flexible surface probe with a layer of liquid crystals which change conformation in a temperature dependent fashion, producing a spectrum of colours representing various temperatures (Flexitherm Inc., Westbury, NY, USA). Electronic telethermography was performed using a Flexitherm Mark V infrared apparatus (Flexitherm Inc.).

Laser Doppler skin flowmetry

Skin blood flow was measured using the LD5 (Med. Pacific Corp., Seattle, USA). A portion of the delivered laser light strikes moving red blood cells and is reflected with a shift in its frequency. The reflected light is analysed in real time by an analog processor that records the instantaneous mean Doppler frequency identified by a square-law detector (Bonner *et al.*, 1981). The laser probe is applied to the skin and the instrument is calibrated for zero flow and the recorder pen is brought to a zero position on the chart paper. The analog output is plotted on chart paper while the voltage output is displayed digitally. A stable baseline is obtained before testing for response to Valsalva manoeuvre, inspiratory gasp, and cold pressure test, as recommended by Low *et al.* (1983).

Quantitative sensory tests

1. Thresholds for warm and cold sensations and for thermal pain (induced by low and by high temperature stimuli) were assessed using the Marstock Thermotest (Somedic AB, Stockholm), as described by Fruhstorfer *et al.* (1976). A Peltier type thermode measuring 2.5 × 1.5 cm was applied to the skin on the dorsum of the right hand, within the area of mechanical hypersensitivity, and on the homologous site of the left hand. The temperature of the thermode could either rise or fall depending on the direction of current flow through the Peltier device. The patient held a switch in his free hand, which he was instructed to press at the first sensation of either warmth, cold, cold pain, or heat pain. Pressing the switch reversed the temperature change, returning to a neutral

temperature of 30° C. An Omniscribe D-5000 strip chart recorder graphically reproduced the results. The patient had no visual access to the digital temperature display or the graphic record.

2. Suprathreshold magnitude estimation of heat-induced pain was assessed during hand immersion in water at temperatures between 36 and 45° C. Temperature steps were 36, 37, 38, 39, 42, and 45° C. The patient was instructed to assign a numerical rating for intensity of pain provoked by hand immersion for 2 s. He chose a scale where 100 represented the worst pain he could imagine, and where 0 represented absence of pain. Suprathreshold magnitude of cold-induced pain was not evaluated.

3. Thresholds for tactile sensation and for mechanical pain were assessed with nylon filaments (von Frey hairs) of equal length and varying diameters (Pressure Aesthesiometer, Stoelting Company, Chicago). The chosen test site was the dorsum of the proximal phalanx of the index finger on right and left hands. Filaments were selected in semirandom order, with 10 successive stimuli applied per filament. The patient reclined with eyes closed, and was verbally cued immediately before each stimulus to ensure adequate attention. He was instructed to report whether he did or did not feel the stimulus, or whether he felt pain. Threshold was expressed in g and measured as the limen between the strongest stimulus not felt in 10 trials, and the weakest stimulus felt (touch or pain).

4. Suprathreshold mechanical pain was induced by light pressure on the dorsum of the proximal phalanx in the right and left index fingers. A pressure algometer (Somedic AB, Stockholm) exerting 200 g over an area of 1 cm^2 was applied for 2 s. The patient moved with his free hand a lever-potentiometer along a visual analog scale, signalling onset, intensity and duration of pain. There were no marks on the scale, but the extreme ends indicated no pain and maximal conceivable pain, respectively. Voltage analogs of the pain ratings in response to mechanical stimuli were stored on magnetic tape (Gould Recorder, model 6500) and displayed on a Tektronix oscilloscope or a Gould ES 1000 Chart Recorder.

5. A square of skin measuring 1 × 1 inches was excized from the hyperalgesic area at the first dorsal interosseous space. It was covered with dermoepidermal skin graft obtained from the patient's thigh (Dr Venkat Rao). Sensory testing was performed at various intervals after grafting.

Nerve blocks

1. Two superficial radial nerve blocks were given on separate occasions by local near-nerve injection of 0.5% bupivicaine, at distal forearm level on the right side.

2. Four sympathetic blocks were performed by injection of 2% lidocaine at the level of the stellate ganglion on the right (Dr Mark Schroeder).

3. Two radial nerve compression blocks were applied. The patient reclined with his right ulnar forearm resting on a padded platform. A 5 cm wide canvas band, with 5 kg weights attached at each end, was placed over the distal radial forearm overlying the superficial radial nerve, localized by palpation. Compression was maintained for 45–60 min. There was no impairment of distal circulation throughout the block. Sensory modalities of touch, cold, warm and pain were monitored by applying light strokes with a soft brush, a cold metal probe, warm air stream and light pressure within the hyperalgesic area (proximal phalanx of the index finger) at intervals of 3–5 min. The patient was instructed to use the lever-potentiometer analog scale to signal pain produced by 200 g/cm^2 pressure applied for periods of 2 s on the proximal phalanx of the index finger as described in the Methods section (quantitative sensory testing, section 4, suprathreshold mechanical pain).

4. Three compression-ischaemia blocks were performed. A sphygmomanometer cuff was placed proximal to the right elbow and inflated well above systolic pressure, to 180 mmHg for 25–40 min. Psychophysical tests were done in the manner described above for radial nerve compression blocks.

Microneurography and intraneural microstimulation

The patient reclined with his arm supported by a padded platform. A lacquer insulated microelectrode, 200 μm in diameter, of the type designed for human microneurography (Vallbo and

Hagbarth, 1968) was inserted manually through the skin into the superficial radial nerve near the junction of the middle and distal thirds of the forearm. A reference electrode was inserted into subcutaneous tissue 1–2 cm outside the nerve trunk. Nerve signals were amplified, audiomonitored, displayed on an oscilloscope (Tektronix 5113) and stored on magnetic tape (Gould Recorder, model 6500) for subsequent analysis.

A switch in the preamplifier permitted the electrodes to connect either to the input of the recording system or the output from a Grass S48 constant voltage stimulator with stimulus isolation unit. For stimulation, square wave pulses of 0.25 ms duration were delivered at frequencies of 1–30 Hz in regular trains of 2 s duration. The amplitudes ranged from less than 0.20 V (for eliciting threshold sensations) to 2 V (for painful stimulation). The pain rating technique using an analog scale (*see* Methods, quantitative sensory tests) was used in conjunction with microneurography and microstimulation. This permitted sensations evoked by natural skin stimulation to be correlated with the recorded neural discharges, and sensations evoked by high intensity intraneural stimulation to be correlated with the duration of the stimulus. The patient was deprived of visual and sound information regarding the stimulus or monitored neural response which might influence his subjective assessment of pain.

During recordings, natural stimuli were applied to the receptive field of any C unit found to be in focus. Such stimuli consisted either of touching the receptive field with cotton wool or a von Frey filament, or briefly and gently stroking the receptive field with a blunt wooden stick.

Seven separate microrecording sessions were performed on the symptomatic right superficial radial nerve, and four on the left.

RESULTS

General findings

The initial examination was performed 14 months after the onset of symptoms. Visual inspection revealed dystrophic changes in the most affected index finger: excessive proximal-to-distal tapering, thin glossy skin with smoothing of skin folds, and thick convex index nail. Neurological examination revealed slightly exaggerated biceps, triceps, and brachioradialis tendon reflexes in the affected limb, not associated with clonus or extensor plantar responses. Strength and muscle tone in the affected limb were normal. Bedside sensory examination revealed normal perception of light touch, vibration, pin prick, joint position sense and two-point discrimination in both lower limbs and in left upper limb. However, in the right upper limb, light touch with a cotton wisp, vibration, or warmth, were all perceived as painful when applied to the dorsum of the index finger. The hyperalgesic area of skin (fig. 1), encompassed the dorsolateral right hand, and the entire index finger (palmar and dorsal surface). Contact thermography revealed the dorsum of the right hand to be consistently warmer by 2–3° C than the left on 5/5 occasions (fig. 2). There was minimal rubor of the skin in the symptomatic area and no sign of tissue injury.

Nerve conduction studies were normal in right median and ulnar, and both superficial radial nerves, and electromyography was unremarkable in the right deltoid, biceps, triceps, flexor carpi radialis, brachioradialis, and cervical paraspinal muscles. Cervical myelography and spinal magnetic resonance images were normal.

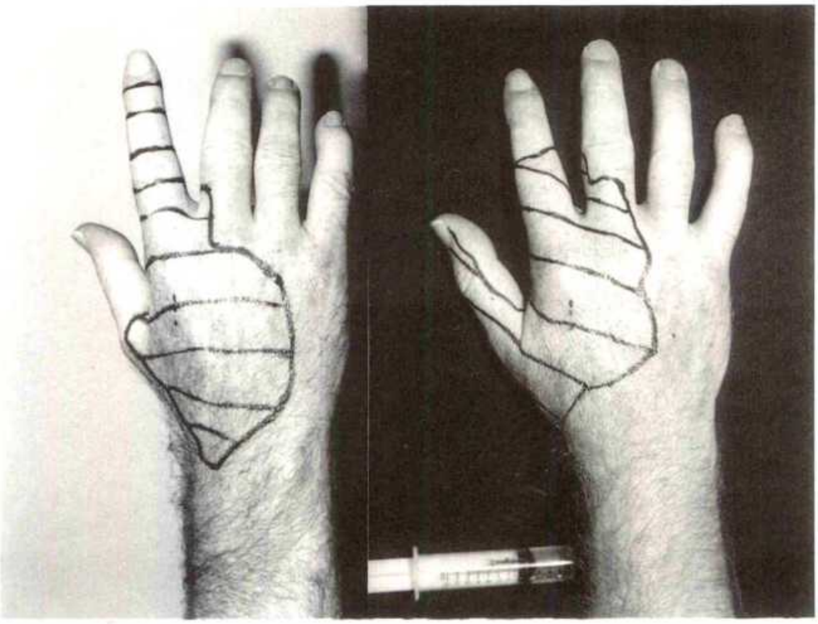

FIG. 1. *Left*, the area of skin manifesting mechanical hyperalgesia is marked on the patient's hand. It encompasses most of the superficial radial and part of median nerve territories. *Right*, local anaesthetic nerve block of the right superficial radial nerve in the distal forearm produced anaesthesia, inclusive of loss of mechanical and heat hyperalgesia, in the marked area.

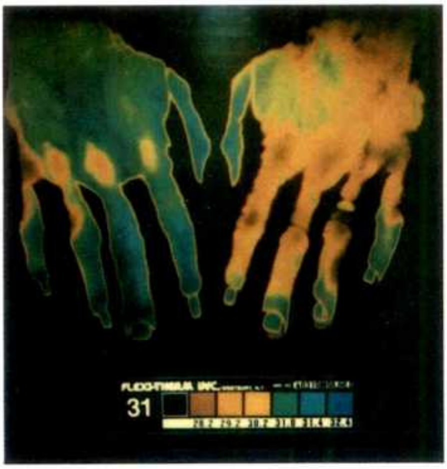

FIG. 2. Contact thermography of the dorsum of both hands. The temperature-colour scale is shown below, with blue being warmer than yellow. The dorsum of the painful right hand was consistently warmer.

Laser Doppler flowmetry, performed in 3 different sites of hyperalgesic skin and corresponding areas of the control hand revealed normal and symmetric blood flow, with a clearcut symmetric reduction in flow upon contralateral hand immersion in cold water, indicating normal somatosympathetic vasoconstrictor reflex response.

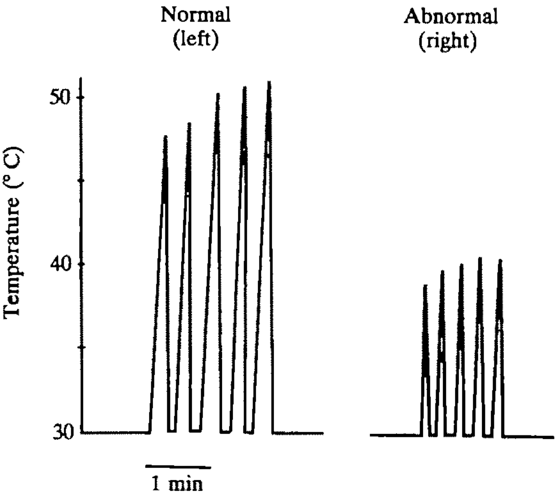

FIG. 3. Heat pain thresholds determined by the Marstock thermotest. A ramp of gradually increasing temperature was applied to the dorsum of the hand via a thermode fixed to the skin. At onset of pain induced by heat the subject pressed a switch which reversed the temperature change. Heat pain threshold in symptomatic skin was some 10° C lower than in control skin on the opposite, unaffected limb.

Quantitative sensory tests

Analysis of detection thresholds for thermal stimuli delivered and measured with the Marstock apparatus, for the right and left hands, revealed normal and symmetric warmth, cold and cold pain thresholds, but heat pain threshold was consistently reduced in symptomatic skin. Heat pain was signalled at much lower temperatures on the right (~40° C) than the left (~50° C) (fig. 3). Study of suprathreshold magnitude estimation of heat pain during immersion of the right hand in warm water for 2 s evoked pain at temperatures which normally do not. Threshold was somewhere between 37 and 38° C. A near maximum pain rating was produced by immersion at 45° C (fig. 4). By contrast, the patient did not signal pain with thermal stimulation of the left hand by immersion at those temperatures.

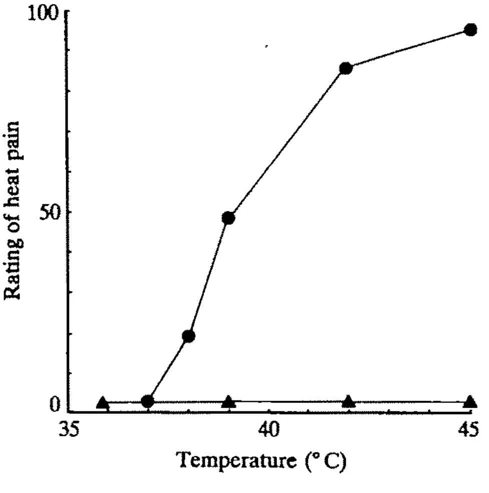

FIG. 4. Suprathreshold magnitude estimate of heat pain. Each hand was separately immersed for 2 s in a water bath at fixed temperatures ranging from 36–45° C. The patient rated the pain induced by this manoeuvre on a scale of 0–100. Closed circles represent pain magnitude for right hand immersion and closed triangles for the left. Suprathreshold heat pain was clearly exaggerated on the right.

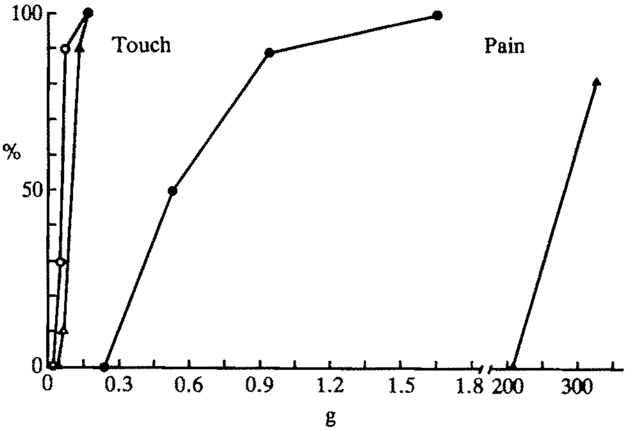

FIG. 5. Touch and pain thresholds measured using nylon monofilaments. The percentage of 10 successive stimuli perceived as touch (open symbols) or pain (closed symbols) is plotted against the applied mechanical pressure. Touch thresholds for the symptomatic right (circles) and normal left (triangles) hand were approximately the same, whereas mechanical pain threshold was much lower on the right hand.

Nylon monofilament testing of touch and mechanical pain thresholds revealed markedly reduced pain thresholds on the affected side, while touch thresholds were approximately the same on both sides (fig. 5). Punctate mechanical pain threshold was between 0.25 and 0.52 g on the dorsum of the proximal phalanx of the right index finger, as compared with a value between 205 and 325 g on the left. Assessment of the suprathreshold subjective magnitude and temporal profile of mechanical pain evoked by 200 g/cm^2 of pressure for 2 s in hyperalgesic skin revealed striking delay, excessive magnitude, and prolonged after-sensation of pain (fig. 6). This mild stimulus, which evoked almost intolerable pain in the symptomatic area, evoked a painless pressure sensation when applied on a

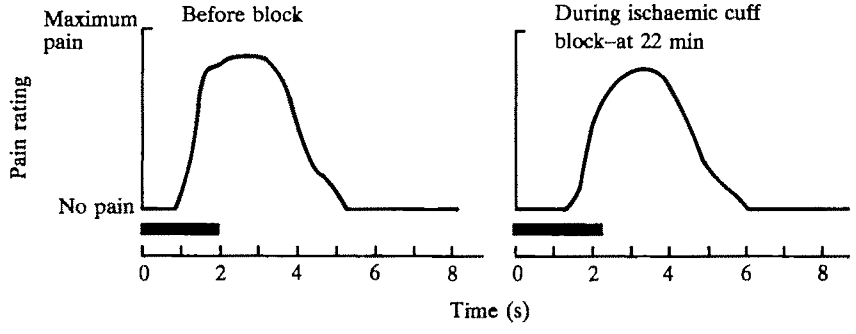

FIG. 6. Suprathreshold mechanical pain in symptomatic skin at baseline and during compression-ischaemia blocks. By operating a manual scale the subject signalled onset, intensity and duration of pain caused by a light mechanical stimulus applied to the right hand for 2 s (solid bars). From symptomatic skin this stimulus evoked severe pain with a latency of approximately 1 s, excessive magnitude, and prolonged after-sensation. The same stimulus in the unaffected left limb was painless. During compression-ischaemia cuff block, at a time when fibre mediated sensations of touch and cold were abolished, the exaggerated pain to a light stimulus remained unchanged, suggesting unmyelinated C fibres are the primary afferent carriers of this pathological pain.

homologous site of the control hand. The reaction time for hyperalgesic mechanical pain (time from stimulus onset to first signal of pain) was long, in the order of 1 s, suggesting that the primary axons mediating hyperalgesia are C fibres. The after-sensation of pain (time between stimulus termination and last sensation of pain) was abnormally prolonged, with pain persisting beyond the stimulus, sometimes by many seconds.

Since the patient reported relief of mechanical hyperalgesia during cooling, pressure algometry was repeated with the symptomatic hand immersed in cold water. At room temperature, threshold for mechanical pain was as low as 100 g/cm^2. A striking elevation in threshold to 4900 g/cm^2 could be consistently induced by immersion in cold water at a temperature that cooled the skin to 10° C. Nevertheless, tactile sensitivity was not convincingly blunted during cold immersion.

Thus psychophysical sensory tests documented mechanical and heat-induced hyperalgesia, with lowered pain thresholds and increased pain magnitude to suprathreshold mechanical and also heat stimuli, together with long reaction time, and prolonged after-sensation. In addition, virtual abolition of mechanical hyperalgesia was observed during cooling.

Sensory testing of the grafted 1 square inch of skin, performed at 119 and 262 days following graft revealed: (1) diminished, but present, tactile sensation in response to light mechanical stimulation using a cotton wisp; (2) presence of touch-pressure sensation to strong mechanical stimulation with pin, but absence of pain; (3) clearly diminished, but present, warmth sensation to stimulation with a warm metallic probe at 40° C; (4) clearly diminished cold sensation to stimulation with a small cold metallic probe at 10° C; and (5) absence of pain sensation to brief noxious heat stimulation with a small hot metallic probe at 50° C. Under these circumstances, there was no mechanical hyperalgesia in response to light touch or pin prick on grafted skin.

Nerve blocks

Local anaesthetic blocks of the right superficial radial nerve at forearm level caused temporary abolition of hyperalgesia, as well as of all submodalities of cutaneous sensation in the superficial radial nerve territory. Hyperalgesia in the distal dorsum and palmar surfaces of the index finger (innervated by the median nerve) was not affected (fig. 2). Further, the radial nerve block made the dorsum of the thumb anaesthetic, an area which was not previously hyperalgesic. Thus hyperalgesia extended beyond pure radial or median nerve territories and was therefore unlikely to be related to mononeuropathy affecting one particular nerve.

Both limb compression-ischaemia and superficial radial nerve compression blocks gave reproducible and concordant results; at a time when myelinated fibre-mediated sensations of touch and cold were no longer present (22 min into compression-ischaemia block and 40 min into compression block) mechanical hyperalgesia remained virtually unchanged (figs. 6, 7). The pain ratings in response

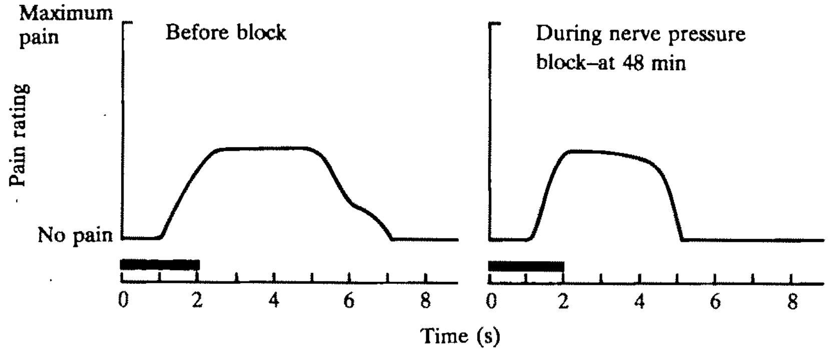

FIG. 7. Suprathreshold mechanical pain in symptomatic skin at baseline (*left*) and during pure compression block of the right superficial radial nerve (*right*). The subject signalled onset, intensity and duration of pain evoked by a light mechanical stimulus applied to symptomatic skin. Solid bars represent stimulus duration. As with compression-ischaemia blocks (fig. 6), pain evoked by light touch persisted when sensations mediated by myelinated fibres were lost.

to mechanical pressure on the dorsum of the proximal phalanx of the index finger appeared at a latency slightly longer than 1 s; the pain was very intense, and typically outlasted cessation of the stimulus by 3 to 4 s. The burning quality of pain induced by weak mechanical stimuli remained unchanged during the blocks. At this stage the patient could still perceive warmth and delayed excessive pain evoked by heat stimuli. This indicates that, in this patient, the peripheral neural impulses mediating hyperalgesia are carried by unmyelinated C fibres.

Following compression-ischaemia blocks, but not after nerve compression blocks, the patient felt tingling paresthaesiae in the hand. Such postischaemic paraesthesiae did not evoke or exaggerate his clinical pain.

Right stellate ganglion blocks produced no convincing change in pain. His hyperalgesia was not improved, as monitored with the pressure algometer and the Marstock Thermotest.

Microneurography and intraneural stimulation

To assess underlying pathophysiological mechanisms more directly, intraneural recordings were performed in the right superficial radial nerve in fascicles supplying hyperalgesic skin. Microneurography revealed the following normal findings: low threshold mechanoreceptor units (3 Pacini, 1 RA, 3 SA-I, 1 SA-II) with receptive fields in hyperalgesic skin had normal receptor response characteristics; intraneural microstimulation in these recording sites evoked tactile sensations but not pain at threshold for detection. Spontaneous and reflexly excited sympathetic efferent neural activity was present and its pattern was qualitatively and quantitatively normal, as conventionally judged on-line.

More importantly, microneurography demonstrated abnormal excitability of C nociceptors. In 11 different recording sites, lightly stroking symptomatic skin produced two distinct peaks of multiunit neural activity with a clearly discernible

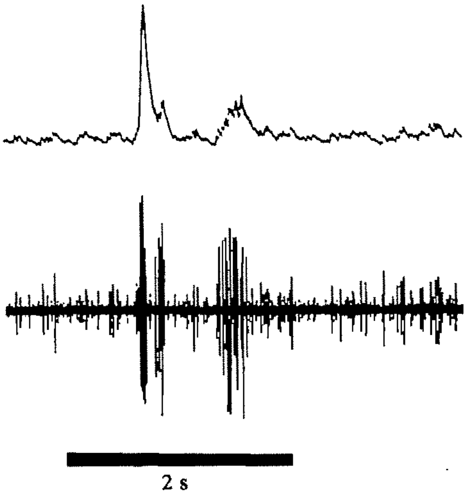

FIG. 8. Lightly stroking symptomatic skin usually evoked not one, but two, distinct initial volleys of neural activity with a clearly definable time interval. The first arises in fast conducting myelinated fibres, the second fits unmyelinated fibre conduction time and reflects the existence of C afferent units with abnormally low thresholds. Sometimes, as illustrated here, a third volley of neural activity corresponding to a sympathetic reflex response with a characteristically longer latency occurred. *Top trace*: integrated neurogram with three elevations. *Bottom trace*: original neurogram.

difference in latency (fig. 8). The first peak was derived from fast conducting myelinated fibres, while the second peak, appearing about 200 ms later for conduction distance of 15 to 17 cm, reflected conduction along very slow, unmyelinated fibres. This second response to light mechanical stimuli suggested the presence of C units with abnormally low receptor thresholds.

When the receptive fields for the twin evoked responses were explored in detail, individual units could be isolated. There C identity was determined from conduction velocities ranging from 0.9 to 1.25 $m \cdot s^{-1}$ (figs 9B, 10). Their afferent identity was established by the method of Hallin and Torebjörk (1974) as follows. While a stable latency value to low-frequency intradermal electrical stimulation is being recorded, the skin receptor is excited with a natural stimulus to provoke a burst. Such repetitive firing slows conduction velocity, which recovers over a short period of time. This manoeuvre documents that a recorded C unit is afferent (fig. 10). Their polymodal identity was evident from their responsiveness to both mechanical and thermal stimuli.

Receptor responses of 5 individual C polymodal nociceptors were studied in some detail. One unit had a particularly low threshold, responding to gentle touching of the receptive field with a cotton wisp (fig. 9C) with one to three discharges per stimulus. Those few discharges were not perceived as painful. The C units not only had abnormally low thresholds to light mechanical stimuli, but also showed extremely prolonged after-discharges. The longest after-discharge observed, evoked by a brief stroke of the unit's receptive field with a blunt stick, lasted for 60 s, while after-discharges ranging from 10–20 s occurred commonly (fig. 11). This stimulus produced severe pain on symptomatic skin, but no pain on the normal left hand. Duration of the discharge of individual C polymodal nociceptors correlated well with the profile of pain rating displayed in visual analog (fig. 12), except for the longest (60 s) after-discharge, which by far outlasted

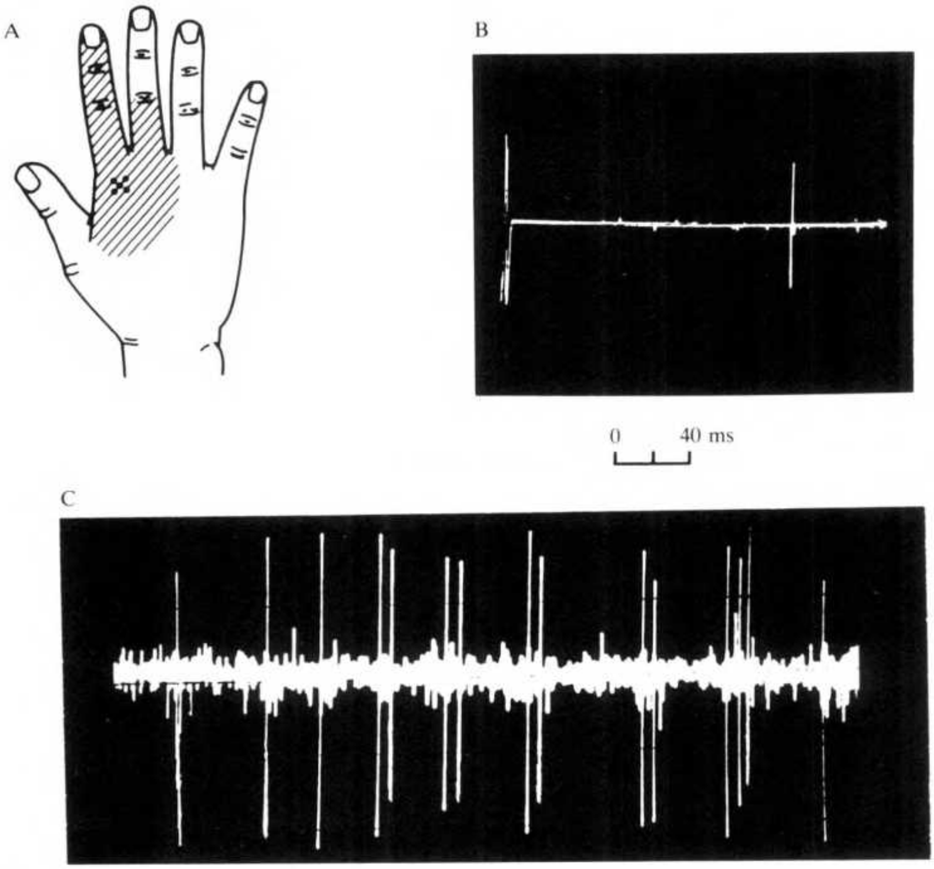

FIG. 9. A, receptive field (RF) for identified C unit (five squares) within the area of hyperalgesia (hatched) contributing to second volley in fig. 8. B, intradermal electrical stimulation in the RF evoked a slowly conducted unitary response (conduction velocity = $1.25\ \mathrm{m{\cdot}s^{-1}}$). C, intraneural recording of C unit response to 9 repetitive light mechanical stimulations of the RF with a wisp of cotton.

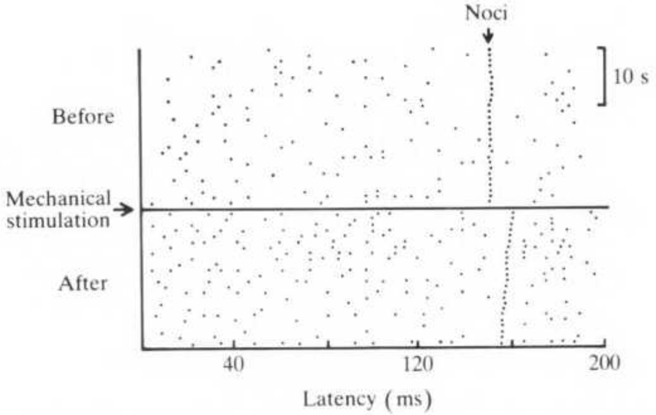

FIG. 10. Dot latency display illustrating afferent nature of individual C nociceptor unit with RF in symptomatic skin. In response to intercurrent application of a mechanical stimulus to the RF, the unit abruptly shifted latency to electrical stimuli.

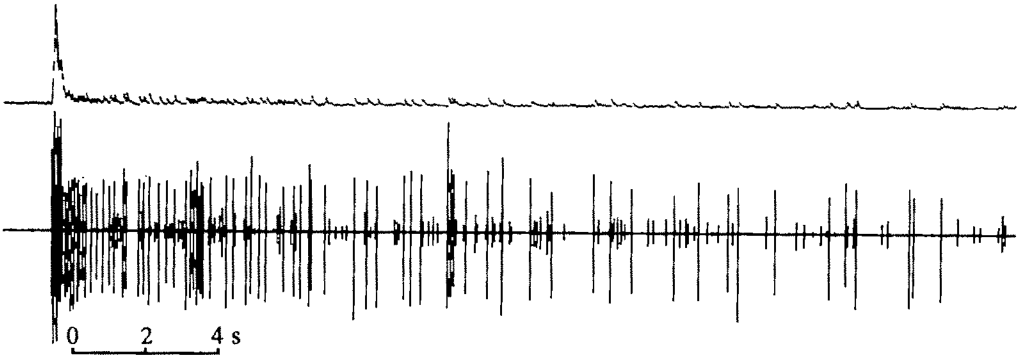

FIG. 11. Abnormally prolonged after-discharge in response to gentle stroking at RF of C unit. *Upper trace*: integrated neurogram; *lower trace*: original neural signals.

the duration of pain. Indeed, the low frequency tail of the after-discharge was not associated with pain. Receptor thresholds for thermal stimuli were not measured for individual C units.

C polymodal nociceptor characteristics in homologous skin of the asymptomatic hand were assessed for control purposes. Lightly stroking the skin evoked normal responses from low-threshold mechanoreceptors, but no afferent C fibre responses. Thus C nociceptor units were less easily identified in normal skin, affirming the aberrant characteristics of similar units in symptomatic skin, where 10 C units were identified in seven experimental sessions. However, a unit with C fibre conduction velocity (1.1 m·s^{-1}) was eventually identified after four recording sessions in the left superficial radial nerve. It responded to moderately intense

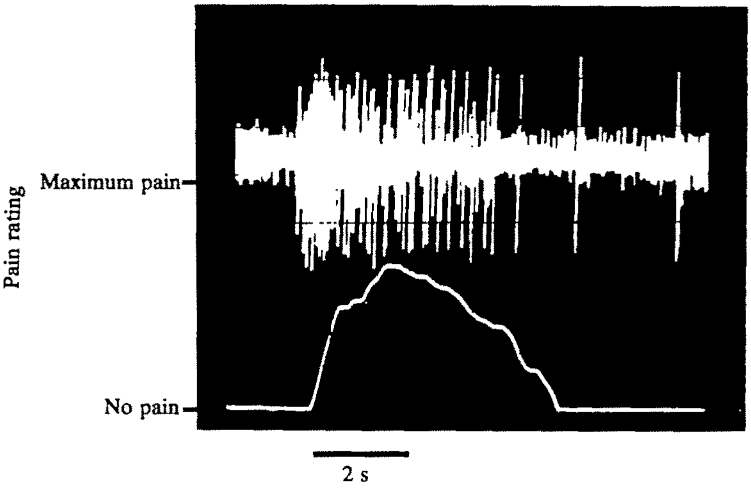

FIG. 12. Correlation between neural discharge of an identified sensitized C polymodal nociceptor with RF in symptomatic skin (*upper trace*) and simultaneous temporal profile of pain magnitude (*lower trace*) in response to gentle stroking of the RF.

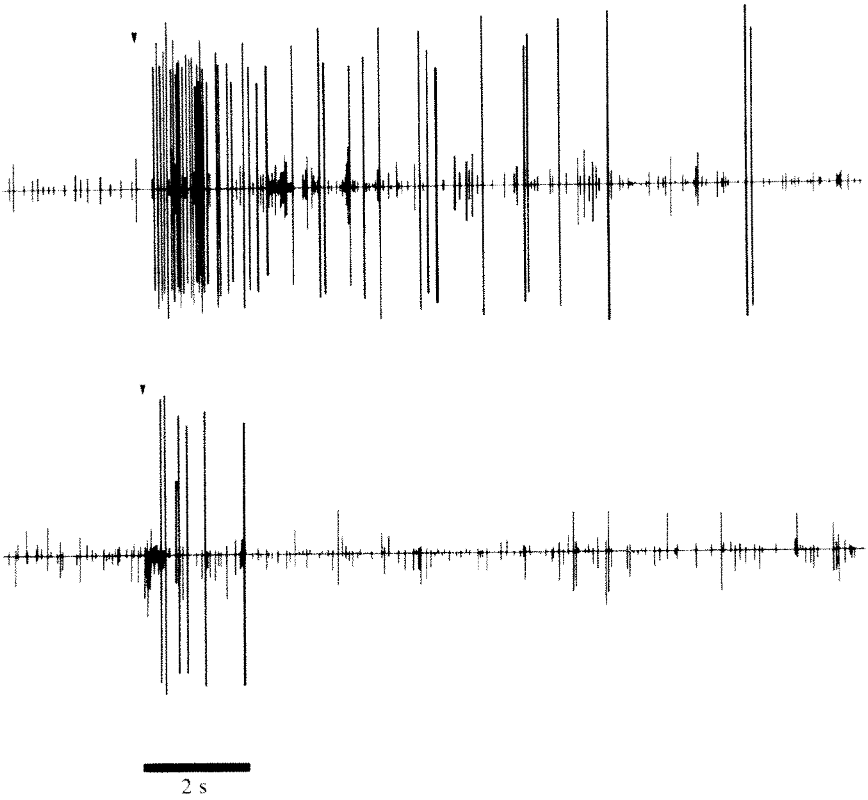

FIG. 13. Response of an identified C polymodal unit in symptomatic skin (*upper trace*) is compared with that from the opposite nonpainful hand (*lower trace*). The mechanical stimulus, stroking with a blunt wooden stick, was applied to the receptive fields, at a time marked by the arrowheads. Note the prolonged after-discharge for the C unit in symptomatic skin.

mechanical and heat stimuli, with brief (1–2 s) after-discharge to mechanical stroking of its receptive field with the wooden stick (fig. 13).

Visual analog pain ratings obtained in response to strong electrical intraneural stimulation of the normal left superficial radial nerve were compared with those obtained when the nerve on the right was stimulated, seeking an index of central processing of pain-evoking neural activity originating from normal and symptomatic periphery. The intraneural electrodes were positioned in the nerve at mid to lower forearm level, approximately 70 cm from the C7 spinous process. Electrode position was adjusted such that severe burning pain from intraneural stimulation was projected to symptomatic skin overlying the dorsum of the second metacarpal bone and proximal phalanx of the index finger, and similar projections of pain were obtained on the contralateral hand. The pain profiles in response to two second trains at 10 Hz were similar on both sides, with latencies of 300–350 ms and after-sensations lasting for a maximum of 1 s, contrasting sharply with the long after-sensation produced by direct receptor stimulation on symptomatic

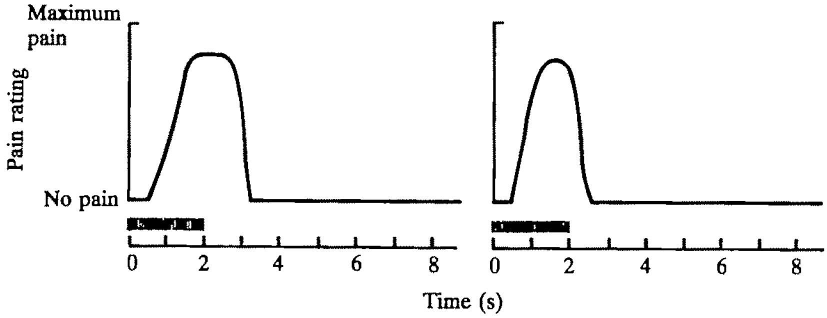

FIG. 14. Temporal profile of pain magnitude evoked by intraneural stimulation at painful intensities in the asymptomatic superficial radial nerve (*left*) is compared with that evoked by stimulation in the symptomatic superficial radial nerve (*right*). Duration of intraneural stimulation is shown above the time scale. The pain profiles were similar.

skin (fig. 14). Thus we could not demonstrate that central processing of afferent input perceived as painful was disturbed for the symptomatic limb.

DISCUSSION

Although this communication revolves around one individual patient, the clinical and basic implications of the results obtained from special investigations are broad. For discussion, they will be categorized as follows. The type of primary afferents conveying the messages ultimately decoded as hyperalgesia will be considered first. This will call for analysis of current arguments concerning central as opposed to peripheral localization of the underlying disorder in the somatosensory system. It will be concluded that, in this patient, hyperalgesia has a primarily peripheral mechanism. The cutaneous receptors of C nociceptive afferents are pathologically sensitized; their unmyelinated fibres overload the CNS with excessive input which is decoded at cognitive levels as exaggerated pain.

Attempts will then be made to interpret the pathogenesis of the basic abnormality in nociceptors and its relationship to the vasomotor signs. While primary sensitization is readily explicable by direct physical injury, perpetuation (and spread) of the process and the accompanying rubor and local warming are probably due to engagement of axon reflexes. Such antidromic activity would trigger neurosecretion at C nociceptor endings of substances which are vasoactive and also able to induce sensitization. Last will follow a discussion of the relation between the clinical syndrome in this patient and reflex sympathetic dystrophy and other clinical conditions with a newly proposed neurogenic antidromic pathogenesis: arthritis, migraine, and the ABC syndrome.

Type of primary afferents mediating hyperalgesia

Both compression-ischaemia and pure nerve compression eventually lead to an experimentally convenient stage of loss of tactile and cold sensory submodalities with preservation of delayed pain and warm sensations. The standard interpretation for this state of dissociated sensory loss is selective conduction block in A beta and A delta myelinated fibres. Classic experiments on local compression-ischaemia of a limb using a sphygmomanometer cuff defined the sequential order of loss of sensory submodalities in space and time, and ascribed the dissociated stage of pain and warm preservation to unimpaired conduction in unmyelinated fibres (Lewis *et al.*, 1931). The correlation was indirect and based on earlier in vivo animal studies by Gasser and Erlanger (1929) (summarized by Gasser, 1935), showing almost complete integrity of the C elevation at a time when A fibre elevations are eliminated by inflation of a sphygmomanometer cuff around a cat limb. The time at which the A fibre potential is blocked in the cat nerve almost exactly coincides with the time when touch-pressure and cold sensations are lost in humans during pneumatic cuff block, while pain and warmth sensations persist beyond 30 min, at a time when only C fibres are conducting (Clark *et al.*, 1935). Direct monitoring of compound nerve action potentials during human limb compression-ischaemia is not available. However, equivalent studies with intraneural microneurographic monitoring have been reported for pure local nerve compression (Torebjörk and Hallin, 1973; Mackenzie *et al.*, 1975). Local nerve compression produces a progressive, time-dependent, loss of sensory submodalities which correlates with conduction block in nerve fibre subpopulations differentiated on the basis of their conduction velocity. Mackenzie *et al.* (1975) and Hallin and Torebjörk (1976) correlated loss of light touch with abolition of function in fibres conducting faster than 30 $\mathrm{m{\cdot}s^{-1}}$ (A beta fibres) loss of cold perception with loss of activity in all myelinated fibres, including A delta fibres; preservation of warmth (although it was impaired) when only C fibre activity remained; and the late reduction in delayed pain with reduction in unmyelinated fibre activity.

Compression-ischaemia blocks combine two variables; compression localized to the nerve directly underneath the cuff, and ischaemia of the entire limb distal to the sphygmomanometer cuff, which affects not only axons but also, potentially, peripheral receptors (Fleminger and Zimmerman, 1976). In addition, because of the arrested circulation, there is a fall in temperature in the ischaemic limb, which in itself could affect receptor excitability (Kunesch *et al.*, 1987). However, compression-ischaemia and pure nerve compression produced similar results in this patient. With either method, there was a stage of dissociated sensory loss featuring abolition of tactile and cold sensations and preservation of warmth and pain sensations.

Thus although neural events were not monitored directly during nerve block in our patient, it can be accepted that during the stage of dissociated sensation, only C fibres were conducting. Therefore, the persistence of hyperalgesia at that stage means that C fibres mediate both mechanical and heat hyperalgesia. This is corroborated by the patient's report that the burning quality of stimulus-induced pain was identical before and during the blocks. In addition, the long reaction times for stimulus-induced pain, of the order of 1 s, indicate that fibres conducting at approximately 1 $m \cdot s^{-1}$ are involved, allowing for a conduction distance of about 80 cm and a central reaction time of at least 150 ms (Price *et al.*, 1977).

The fact that hyperalgesia persisted virtually unchanged in magnitude and duration during A fibre block indicates, as a complement, that A fibres do not contribute appreciably to the hyperalgesia in this patient. This conclusion is supported by the additional observation that postischaemic paraesthesiae, projected to the hand, did not revive clinical pain. It has been shown by direct microneurographic recordings in man that postischaemic paraesthesiae are due to high frequency ectopic impulse generation in myelinated fibres only (Torebjörk *et al.*, 1979; Ochoa and Torebjörk, 1980). That such a massive discharge in A fibres was not painful in the patient argues against A fibre involvement in the pain syndrome. Further support comes from the observation that intraneural microstimulation, at threshold intensity for detection, evoked tactile rather than painful sensations when performed in fascicular sites where low-threshold mechanoreceptor units were recorded. This is the normal behavioural result of intraneural microstimulation in healthy volunteers (Torebjörk and Ochoa, 1980; Ochoa and Torebjörk, 1983; Schady *et al.*, 1983; Torebjörk *et al.*, 1987).

Based on these several lines of evidence, we conclude that C fibres are the primary afferents coding for hyperalgesia in this patient.

The basic abnormal somatosensory mechanism

Microneurographic recordings in radial nerve fascicles supplying hyperalgesic skin disclosed normal function of low-threshold mechanoreceptors, but abnormally excitable C polymodal nociceptors. Their C identity was established by conduction velocity measurements of around 1 $m \cdot s^{-1}$, and polymodal responsiveness was evident from their activation by heat and mechanical stimuli. These C units had abnormally low thresholds to stimuli, such as gentle contact of the skin with cotton wool, which normally do not excite C nociceptors in human skin (Torebjörk, 1974, 1985; Torebjörk and Hallin, 1974, 1976). In addition, a brief stroke across their receptive field induced prolonged after-discharges for up to 1 min, a finding not encountered in normal human C nociceptors, which only discharge for a few seconds beyond stimulus termination (Torebjörk and Hallin, 1974). Thus the enhanced responsiveness of C polymodal nociceptors in this patient is abnormal not only in respect to what is known in the experimental literature, but also in comparison with a control C polymodal nociceptor in the same individual—the one supplying a homologous area of skin of the asymptomatic hand.

The findings of abnormally lowered threshold and exaggerated discharge are consistent with cutaneous C nociceptor sensitization, as previously described in acute experiments in several species—rat (Lynn and Carpenter, 1983), rabbit (Fitzgerald, 1979; Lynn, 1979), cat (Bessou and Perl, 1969; Beck *et al.*, 1974), monkey (Beitel and Dubner, 1976; Croze *et al.*, 1976; Kumazawa and Perl, 1977; Campbell and Meyer, 1983) and man (Torebjörk and Hallin, 1977; Torebjörk, 1979; Torebjörk *et al.*, 1984*a*). However, chronic sensitization, or sensitization associated with a human clinical disorder has never before been documented.

Relationship between abnormal receptor mechanisms and abnormal sensation of pain

The correlation observed between C nociceptor discharge and suprathreshold profile of pain rating in response to gentle skin stimulation reasonably indicates that excessive magnitude and duration of pain in this patient were induced by massive recruitment of excessively sensitive C nociceptors that exhibited prolonged after-discharge. However, the enhanced responsiveness of individual C nociceptors was not necessarily congruous with the patient's reports of pain. Just a few single unit discharges triggered by cotton wool touching the skin did not correlate with perceptible pain, and the 1 min after-discharge of diminishing rate in an individual C unit was accompanied by pain for only part of it. This is not surprising in view of previous studies showing that one to several impulses in a single C unit need not be felt (Torebjörk and Hallin, 1974), and that spatial and temporal summation of the nociceptive inflow is necessary to reach pain threshold (Torebjörk, 1981). In other words, subjects base their detection and magnitude rating of pain on the population response from C nociceptors activated by natural stimuli, rather than just on the input from an individual C nociceptive fibre which happens to be in focus for microelectrode recording (Van Hees and Gybels, 1981; Torebjörk *et al.*, 1984*a*). Thus on the overall basis of the abnormal nociceptor response characteristics, coupled with the long reaction times and the outcome of differential nerve blocks, we conclude that chronic sensitization of cutaneous C polymodal nociceptors in this patient determines hyperalgesia to mechanical and heat stimuli.

An additional abnormality of central processing?

In view of the proposal that certain forms of hyperalgesia following peripheral nerve injury result from secondary central nervous dysfunction (Lindblom and Verrillo, 1979; Ochoa, 1982; Fruhstorfer and Lindblom, 1984; Wall, 1984; Meyer *et al.*, 1987), it was thought important to ascertain whether in this patient an additional disorder of central sensory processing existed. This issue was addressed by directly questioning the brain about comparative quality and magnitude of pain evoked from the peripheral sensory apparatus projecting to symptomatic and control skin. But pain was evoked by means of intraneural stimulation, after bypassing the known sensitized nerve endings. It was necessary to use stimulus intensities high enough to cause severe burning pain. Experiments in which one set of distal microelectrodes was used for intraneural stimulation and another set of electrodes, placed proximally in the same nerve fascicle, recorded propagated nerve impulses, have shown that massive responses both in A and C fibres are elicited when severe burning pain is reported (Torebjörk *et al.*, 1984*b*), and that excitation failure is not likely to occur in any fibre population at the stimulus frequency (10 Hz) and train duration (2 s) used in the present study. Thus it can be accepted that the stimulus parameters used were adequate for A and C fibre stimulation. The fact that no convincing differences were observed in latency, temporal profile and duration of pain ratings in response to stimulation from either side, argues against pathological central processing of afferent signals from the hyperalgesic area. The observed after-sensation of pain which outlasted cessation of the stimulus train by about 1 s is explained by slow conduction in the ascending afferent C volley and by some temporal summation at central levels, observed also in normal subjects (LaMotte *et al.*, 1984). Albeit intense, the pain induced from the right radial nerve was not excessive in comparison with pain induced from the normal side. Thus the evidence does not support the possibility that hyperalgesia in this patient's hand is due to a sizeable abnormality in central processing of afferent signals.

Against the peripheral explanation in this patient stands the theoretical argument favouring a CNS abnormality as *necessarily* responsible for human hyperalgesia as a symptom of disease. Wall (1984) advocated the central hypothesis, noting several factors which, in his opinion, preclude a peripheral mechanism for the syndrome. Several of these are recounted here, counterpointed by documentable peripheral explanations: 'No recordings from normal or damaged nociceptors have shown the expected signs of summation or long latency and prolonged afterdischarge which would be required to explain the sensory experience'; 'the duration of sensation does not match the stimulus'; the rapidity with which the syndrome occurs following trauma has 'no peripheral correlate'; the failure of nerve grafts to cure the symptom once the graft has reinnervated its target tissue; and morphophysiological changes occurring in spinal cord organization following experimental manipulation of peripheral nerves.

The first point, that expected changes in nociceptors have not been found is now outdated (Cline and Ochoa, 1986); they are illustrated and amplified in this publication. Pain which outlasts the stimulus has a peripheral explanation in our patient, in light of the observed prolonged after-discharges from sensitized nociceptors. If sensitized nociceptors are responsible for the syndrome, it is no surprise that the onset of symptoms following injury may be quite rapid, because C nociceptors in man are capable of becoming sensitized within minutes following noxious stimulation (Torebjörk and Hallin, 1977; Torebjörk *et al.*, 1984*a*). The idea that delayed failure of nerve graft therapy indicates a central dysfunction ignores a reasonable peripheral explanation: nociceptors whose sensitized state cannot be expressed symptomatically when the skin is denervated, might recreate the painful symptoms when reinnervating their target. Thus the nerve graft argument weakens, and is further questioned by results of the skin graft, as described above. Finally, the fact that central changes occur with various manipulations of the peripheral nervous system does not eclipse the body of knowledge about receptor hyperexcitability following manipulation of the same peripheral system.

We certainly do not imply that every case of hyperalgesia is explained at peripheral nociceptor level. Psychophysical tests measuring very short reaction times for pain in patients with allodynia and hyperalgesia following nerve injury (Lindblom and Verrillo, 1979; Fruhstorfer and Lindblom, 1984) and rapid abolition of hyperalgesia during compression-ischaemia block (Wallin *et al.*, 1976; Torebjörk and Hallin, 1979; Ochoa, 1982; Meyer *et al.*, 1985; Meyer *et al.*, 1987) suggest abnormal central processing of afferent signals mediated by fast conducting fibres. But that evidence does not imply either that every case of hyperalgesia is explained at a central level.

Nature of the regional vasomotor changes: their relevance to the pathogenesis of cutaneous receptor sensitization

Symptomatic skin on the dorsum of the patient's right hand exhibited faint rubor and was 3-4° C warmer than normal skin on the left hand. It is unlikely that the vasodilatation underlying those physical signs is due to partial vasoparalysis caused by a defect in sympathetic vasoconstrictor supply. In fact, there was no abnormality of sympathetic efferent neural activity as documented by microneurography. Further, in this and other patients with equivalent clinical syndromes, the possibility that the smooth muscle effector may have been unresponsive to vasoconstrictor neural outflow has been excluded by laser Doppler capillary flow measurements (Ochoa, 1986; Ochoa *et al.*, 1987*a*). The alternative possibility that the objective skin signs are actively induced by antidromic vasodilatation (Bayliss, 1901; Hinsey and Gasser, 1930; Foerster, 1933) is more appealing, especially because such a mechanism can tie together the abnormal vasomotor and the sensory receptor phenomena observed (Lewis, 1936*b*; Jung, 1941). From this study we can neither provide direct evidence for antidromic activity in C nociceptors nor for participation of nociceptor neurotransmitters in the pathogenesis of the vasomotor signs or abnormal receptor mechanisms. However, a wealth of indirect evidence supports this concept. For example, antidromic stimulation of the sensory supply to human skin, at painful intensities, induces regional vasodilatation which is independent of the autonomic system (Foerster, 1933; Ochoa *et al.*, 1987*b*). Similar treatment in experimental animals induces vasodilatation and plasma extravasation (Lembeck and Holzer, 1979; *see also* Chahl *et al.*, 1984), detectable even when single nociceptors are stimulated (Kenins, 1981). Importantly, such experimental antidromic stimulation also induces sensitization of cutaneous receptors (Chahl and Ladd, 1976; Fitzgerald, 1979).

Further indirect evidence for an antidromic event-related pathogenesis of both vasomotor and receptor anomalies comes from experiments using capsaicin (Jancsó *et al.*, 1967; Lembeck, 1983). In man, experimental application of capsaicin induces an acute clinical syndrome remarkably similar to the one under discussion (Ochoa, 1986; Ochoa *et al.*, 1987*a*). This neurotoxin specifically targets on substance P-containing neurons. It causes release of substance P which triggers a neurohumoral cascade at peripheral levels, leading both to vasodilatation and C nociceptor sensitization in animals (*see* Chahl *et al.*, 1984) and in man (Konietzny and Hensel, 1983).

Evolution of receptor sensitization into chronicity might reflect resetting of the transducer mechanisms at a new steady-state, as a direct consequence of the primary physical injury. Alternatively, it may reflect a dynamic change in receptor excitability actively sustained by a vicious circle. Actually, two superimposed vicious circles might operate. First, sensitized nociceptors firing spontaneously (or excessively) may, via axon reflexes, trigger antidromic neurosecretion from their branches, thus boosting receptor sensitization. Secondly, skin warming, induced by the vasoactive neurotransmitters, may enhance the strikingly temperature-dependent excitability of the abnormal nociceptors.

Earlier writings incriminated antidromic activity in primary nociceptors as responsible for neuropathic painful syndromes associated with vasomotor effects in man (Jung, 1941; Chapman *et al.*, 1961). Lewis (1936*a*) placed this activity in 'nocifensor' nerves which he postulated served an efferent protective function, responsible for flare and hyperalgesia surrounding local skin injury. While still awaiting direct evidence of antidromic discharge, the present demonstration of sensitized nociceptors in one patient with hyperalgesia and skin warming helps consolidate those ideas.

Relationship of nociceptor sensitization to reflex sympathetic dystrophy and other painful neurological syndromes

The present case cannot be classified in any standard diagnostic category to total satisfaction. The causalgic burning quality of the pain, the associated mechanical hyperalgesia, and the trophic skin change, certainly justified the referring diagnosis of reflex sympathetic dystrophy. Failure of sympathetic blocks to relieve the symptoms is said not necessarily to invalidate this diagnosis when blocks are performed in patients in chronic stages (Bonica, 1979), and on descriptive grounds the case remains legitimately one of reflex sympathetic dystrophy. However, in this patient, evidence points to a normally functioning sympathetic system: skin blood flow measurements indicating normal vasoconstrictor capacity in symptomatic skin; and microneurographic recordings revealing an apparently normal pattern of spontaneous and reflexly induced sympathetic discharge. Considering that the basic abnormal mechanism underlying the sensory syndrome in this patient is clarified, and that a related explanation is available for the associated physical signs, it may be more pertinent to ask whether (at least some) patients with reflex sympathetic dystrophy in reality have this patient's syndrome, rather than asking the reverse. Indeed, this case can be regarded as resulting from a primary disorder of peripheral nociceptors masquerading as reflex sympathetic dystrophy. It is unlikely that the situation is unique for the patient under discussion; in fact, the same seems to be the case for a recently described subgroup of patients also featuring burning pain associated with hyperalgesia, and vasomotor skin changes (Ochoa, 1986; Ochoa *et al.*, 1987*a*). Although direct recording of sensitized nociceptors is not available in those patients, clinical criteria were proposed as pathognomonic equivalents of nociceptor sensitization. Together with hyperalgesia to mechanical and warm energy, and similar to the capsaicin model, those patients also experienced dramatic and rapid abolition of both spontaneous pain and mechanical hyperalgesia with passive cooling (Ochoa, 1986).

The relief of mechanical hyperalgesia by cooling is probably not explained through a normal central inhibitory mechanism elicited by activation of myelinated fibres (Bini *et al.*, 1984), since reduction, or even abolition, of mechanical hyperalgesia by cooling has been observed in this and in other patients even when conduction in A fibres is blocked (Ochoa, 1986; Ochoa *et al.*, 1987*a*). Instead, cooling may reduce the excitability of experimentally sensitized C nociceptors (Kumazawa *et al.*, 1987) in a way perhaps related to the reduced responsiveness of normal C nociceptors by cooling human skin (Kunesch *et al.*, 1987). This behaviour sharply contrasts with the facilitation caused by cooling of ectopic discharge generated in C axons in experimental nerve-end neuromas (Matzner and Devor, 1987).

In a broad sense the present syndrome can be regarded as an expression of neurogenic inflammation. Such a process begins to emerge as pathogenetically significant in other clinically unrelated conditions, such as arthritis (Levine *et al.*, 1985*a*, *b*) and migraine (Moskowitz *et al.*, 1986; Markowitz *et al.*, 1987). Future therapy directed at the control of neurogenic inflammation (*see* Chahl *et al.*, 1984) or at desensitization of receptors (*see* Chalazonitis and Gola, 1987) should prove beneficial for these patients.

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DELAY IN THE EXECUTION OF VOLUNTARY MOVEMENT BY ELECTRICAL OR MAGNETIC BRAIN STIMULATION IN INTACT MAN

EVIDENCE FOR THE STORAGE OF MOTOR PROGRAMS IN THE BRAIN

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SUMMARY

Experiments were undertaken to study the effect on voluntary movement of an electrical or magnetic stimulus delivered to the brain through the scalp. Subjects were trained to flex or extend their wrist rapidly in response to an auditory tone. A single brain stimulus (electrical or magnetic) delivered after the tone and before the usual time of onset of the voluntary reaction could delay the execution of the movement for up to 150 ms, without affecting the pattern of the agonist and antagonist EMG bursts. The delay increased with increasing stimulus intensity and with stimuli which were applied nearer to the usual time of onset of the voluntary reaction. A stimulus given after the onset of the first voluntary agonist EMG burst only delayed the onset of the first antagonist and later EMG bursts. Movement was not delayed when similar experiments were performed with supramaximal stimulation of the median nerve instead of the brain stimulus.

The delay following a cortical shock was not due to spinal motoneurons being inaccessible to descending input during the delay period since a second brain stimulus, given in the middle of the delay period, was capable of producing a direct muscle response. Neither could the delay be explained by the brain stimulus altering the time of the subject's intention to respond since a stimulus delivered to one hemisphere before an attempted simultaneous bilateral wrist movement produced a far greater delay of the contralateral than the ipsilateral movement. We suggest that the brain stimulus delayed movement by inhibiting a group of strategically placed neurons in the brain (probably in the motor cortex) which made them unresponsive for a brief period to the command signals they receive which initiate the motor program of agonist and antagonist muscle activity. The results have implications for the issues of the storage of motor programs, internal monitoring of central movement commands and the site of organization of the antagonist EMG burst.

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INTRODUCTION

In view of the number of cortical elements that may be excited by an electrical shock to the brain (Phillips and Porter, 1977), it is perhaps surprising that, in man, a single stimulus delivered through the scalp produces no readily observable effects other than elemental movements or visual phosphenes (Merton and Morton, 1980). Thoughts, sensations and complex movements have not been elicited. It may be that such a nonspecific and nonpatterned stimulus is more likely to disrupt, than to mimic, complex aspects of normal brain activity. Indeed, interruption of normal brain activity is observed quite frequently following stimulation of the exposed cortex during neurosurgical procedures. For example, repetitive 60 Hz stimulation of precentral cortex may not only evoke contralateral movements of the body but also halt ongoing voluntary movement and produce a feeling of paralysis (Penfield and Jasper, 1954). The present experiments were designed to explore some 'negative' effects of a single brain stimulus; in particular to see whether the processing involved in the preparation and execution of a simple motor reaction task could be affected. The results show that when moving in response to an auditory stimulus, the movement is not abolished but may be delayed by an appropriately timed stimulus delivered to the brain through the scalp. It is as if part of the brain and the information contained within it had been frozen for a brief period. The results have important implications for theories of the central organization of motor programs. A preliminary communication of the early results has been published (Day *et al.*, 1987).

METHODS

The following procedures were performed with the approval of the local ethical committee on 8 normal volunteers (aged 28–38 yrs), including the authors. The subject was seated with shoulder abducted and elbow flexed so that the forearm rested on a horizontal platform placed next to the chair. The forearm was semipronated and clamped to the platform. The hand, with fingers extended, was encased in a rigid splint which was free to rotate in the horizontal plane about an axis which was coaxial with that of the wrist. Rotation of the splint and hand was transduced by a potentiometer. Subjects were requested to perform a rapid isotonic wrist flexion (or extension) movement of about 20°. The position of the wrist was displayed to the subject on an oscilloscope screen as the horizontal position of a 2 cm vertical line. The procedure was as follows. The wrist position marker on the screen was blanked for a period of 0.7 s to warn the subject that a trial was about to begin and 1 s later in 75% of the trials a 1 kHz tone was delivered through the headphones for a duration of 100 ms. The tone acted as a signal for the subject to perform the rapid wrist movements. Subjects practised this procedure for 10–15 min (intertrial period of 10 s) with their previous movements being displayed to them. Subjects were encouraged to be as consistent as possible and to minimize the variability in reaction time. These trials were not collected. When the subject was sufficiently practised the experiment began. The procedure was repeated except during one-third of the trials in which a tone to move was given, a brain stimulus was given also at a preset time relative to the tone. Subjects were instructed to ignore the brain stimulus and to move as before. In one series of experiments subjects were required to make bilateral symmetric wrist movements. For these experiments both hands were placed in identical splints.

Two noninvasive methods were used to excite the brain. Electrical stimuli were delivered to the scalp using a prototype capacitative discharge device (700 V maximum, 50 μs time constant) built by Mr. H. B. Morton. The capacitor was discharged via two standard 9 mm disc EEG electrodes fixed to the scalp with collodion. Usually the cathode was placed at the vertex and the anode 7 cm laterally on a line joining the vertex to the external auditory meatus. This electrode configuration was used when studying movements of the contralateral arm only. In some experiments (*see* below) movements of both arms were studied; it was then important to minimize current flow to the opposite motor cortex. To achieve this the cathode was moved from the vertex position to a point 7 cm anterior to the vertex. This allowed relatively pure stimulation of one hemisphere which produced only small (or absent) muscle responses in the ipsilateral arm. The second method of brain stimulation was achieved using a prototype magnetic stimulator built by Dr. A. Barker and colleagues of the Medical Engineering Department of Sheffield University (Barker *et al.*, 1985). A pulsed magnetic field (2.1 T maximum at 230 μs) was applied via a 9 cm mean diameter flat coil which was held on the head, usually with its centre overlying the vertex. When studying bilateral wrist movements the coil was held on the side of the head with its centre overlying a position 4 cm anterior to a point 7 cm lateral along a line joining the vertex to the external auditory meatus. For both types of stimulator, intensity is expressed as a percentage of the maximum output of the device.

Electromyographic (EMG) activity was recorded from wrist and finger flexor and extensor muscles in the forearm via pairs of Ag-AgCl surface disc electrodes placed 2-3 cm apart. EMG signals were preamplified and filtered (Devices type 3160; 3 dB points at 80 Hz and 2.5 kHz) and further amplified (Devices type 3120). The signals were then rectified, smoothed and digitized with a sampling rate of 500 Hz per channel. Data were collected and stored using a PDP 12 computer.

RESULTS

Brain stimulation delays a fast voluntary movement

The rapid wrist movements studied here were characterized by a stereotyped agonist-antagonist-agonist pattern of activity in flexor and extensor muscles. For the subject illustrated in fig. 1 the reaction time (measured as the interval from auditory tone to onset of first agonist EMG burst) was 136±3 ms (mean±SEM). In random trials a brain stimulus was applied 100 ms after the tone to the contralateral hemisphere at an intensity sufficient to produce a flexor muscle response just before the *expected* time of onset of voluntary EMG activity. In these trials the pattern of voluntary muscle activity remained the same as in control trials but the reaction time was increased by some 50 ms to a value of 185±5 ms. This effect was seen in all subjects and was apparent with both electrical as well as with magnetic brain stimulation.

The amount by which the voluntary movement was delayed was related to the brain stimulus intensity, although for a given stimulus intensity the amount of delay varied appreciably between subjects (e.g., using a magnetic stimulus of 70%, the delay ranged from 0-163 ms (mean 64±22 ms) in 6 subjects). In fig. 2, the time of onset of the first agonist burst after the audio signal has been plotted against the time of onset of the first antagonist burst from individual trials of one subject. Data from control trials and from trials in which a magnetic stimulus of 60%, 70% or 80% was given 60 ms after the tone are plotted by different symbols.

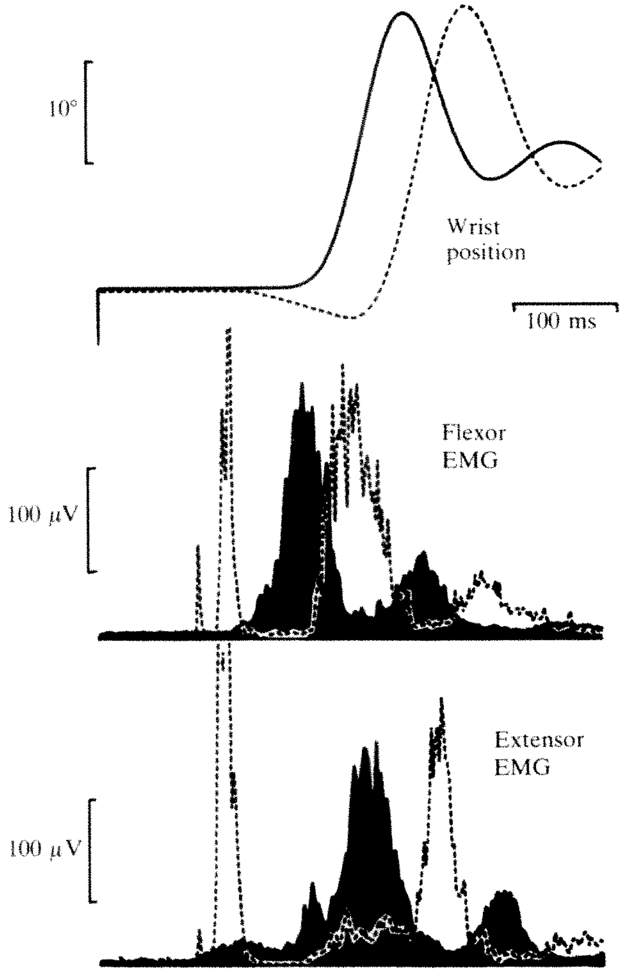

FIG. 1. Rapid wrist flexion movements in a single normal subject in response to an audio signal given at the start of the sweep, with (dotted lines) and without (solid traces) magnetic cortical stimulation delivered 100 ms after the start of the sweep. Shown are average wrist position (*upper traces*, flexion upwards), wrist and finger flexor (*middle traces*) and extensor (*lower traces*) rectified EMG activity. The control movement (average of 26 trials) is characterized by alternating bursts of activity in the flexor and extensor muscles. In those trials in which a cortical stimulus was given (70% magnetic stimulation, average of 10 trials) the movement and associated pattern of muscle activities are the same but delayed by some 60 ms. Note the direct muscle responses in the flexor and extensor muscles occurring some 15 ms after the stimulus artefact producing, in this case, a small extension movement seen in the wrist position trace.

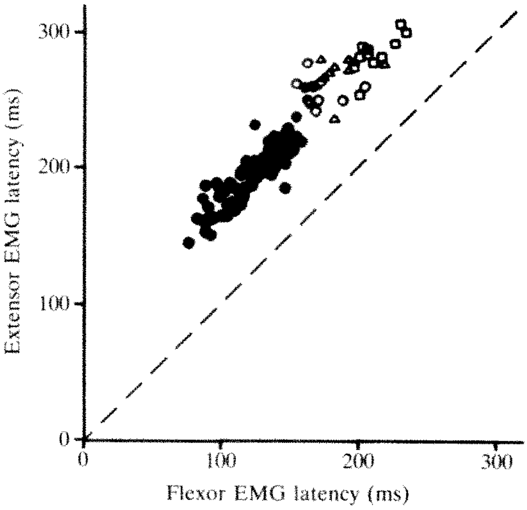

FIG. 2. The latency (measured from the audio signal) to onset of wrist flexor (agonist) EMG activity plotted against the onset of wrist extensor (antagonist) EMG activity for individual trials of a series of wrist flexion movements made by one subject. Control trials (denoted by closed circles) and trials with an interposed magnetic cortical stimulus (60 ms after the tone) at different intensities of stimulation are shown by open symbols (open circle denotes 60%, triangle 70%, square 80%). The delay in onset of EMG activity in forearm muscles produced by each stimulus during wrist flexion movements is similar for both flexor and extensor muscle groups, and increases with higher intensities of stimulation.

In control trials, the mean reaction time of the agonist burst was 125 ms although individual values varied by some 80 ms. The first antagonist burst followed the agonist onset after approximately 60 ms. In those trials in which a brain stimulus was given, the reaction time to onset of both the voluntary agonist and antagonist bursts was increased by an amount which depended upon the stimulus intensity. The higher the intensity the greater was the delay. Whatever the intensity of stimulation, the increase in reaction time was the same for the antagonist muscle as for the agonist.

Preservation of the pattern of intended muscle activity following a brain stimulus was demonstrated further by the following experiment. In the first half of this experiment the subject was asked to make a rapid wrist flexion movement in response to an auditory signal. In the second half, a rapid wrist extension movement was required. Fig. 3A shows the averaged EMG activities in the flexor and extensor muscles of the wrist with and without interposed cortical stimuli given 50 ms after the audio tone. The times of onset of the first flexor and first extensor bursts in the individual trials have been plotted in fig. 3B. For the wrist flexion movement the flexor burst preceded the extensor burst, whereas for a wrist extension movement the extensor burst preceded the flexor burst. When a brain stimulus was given the flexor/extensor relationship was preserved for both movements, although the complete pattern was delayed.

These results show that a single brain magnetic stimulus can interfere with processes underlying the production of a simple movement during a reaction task. Identical results were obtained with electrical stimuli (fig. 4). The effect is to delay the initiation of movement without affecting the organization of the pattern of agonist/antagonist muscle activities. The delayed triphasic EMG pattern is not merely a complex series of late muscle contractions which follow the early direct muscle response to the cortical stimulus, since the order of flexor and extensor bursts depends critically upon the subject's intent.

Comparison with a peripheral nerve stimulus

In tonically active muscles, a brain stimulus produces a response followed by a period of silence in the electromyogram similar to that observed following a peripheral nerve stimulus. Experiments were carried out to see whether a peripheral nerve stimulus was capable of delaying movement onset in the same way as a brain stimulus. Fig. 4 illustrates the averaged agonist muscle activity from a subject attempting to flex the wrist rapidly in response to an auditory tone. As before, when an electrical brain stimulus was interposed between the tone and normal movement onset, the first agonist burst was late and the movement was delayed. In contrast, the first agonist burst was made smaller but was not delayed by a supramaximal median nerve electrical stimulus delivered at the elbow so as to produce a direct muscle response in the wrist flexor muscles at a time comparable with that produced by the brain stimulus. The reduction of the agonist burst may have been due to inhibitory effects acting on the spinal motoneurons from various

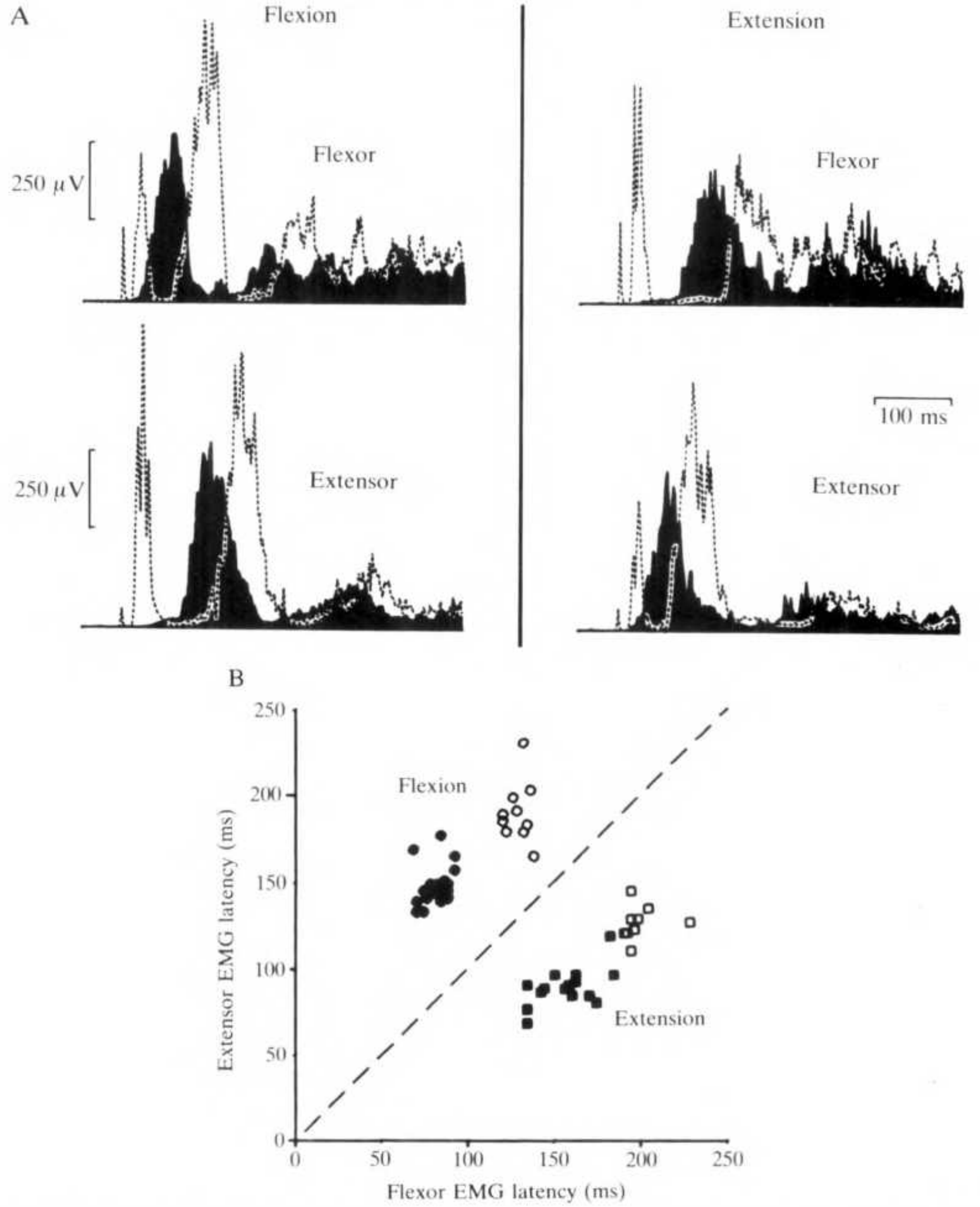

FIG. 3. A, average wrist flexor and extensor rectified EMG activities associated with rapid wrist flexion (*left panel*) and wrist extension (*right panel*) movements from one subject in response to an auditory signal at the beginning of the trace. Solid traces refer to control trials (n = 18) and dotted lines to those trials (n = 10) in which a 63% magnetic cortical stimulus was given 50 ms after the audio tone, before the expected time of onset of the first agonist EMG burst (note stimulus artefact and direct muscle responses). For both flexion and extension movements the cortical stimulus delays their execution but does not disrupt their unique sequences of muscle activation. B, the flexor and extensor EMG onset latency are plotted from individual trials of the same movements as in A. Flexion movements are represented by circles and extension movements by squares. Control movements are shown by closed symbols and movements preceded by a cortical stimulus by open symbols. The relative timing of the EMG burst are preserved although delayed by some 50 ms when a cortical stimulus is given.

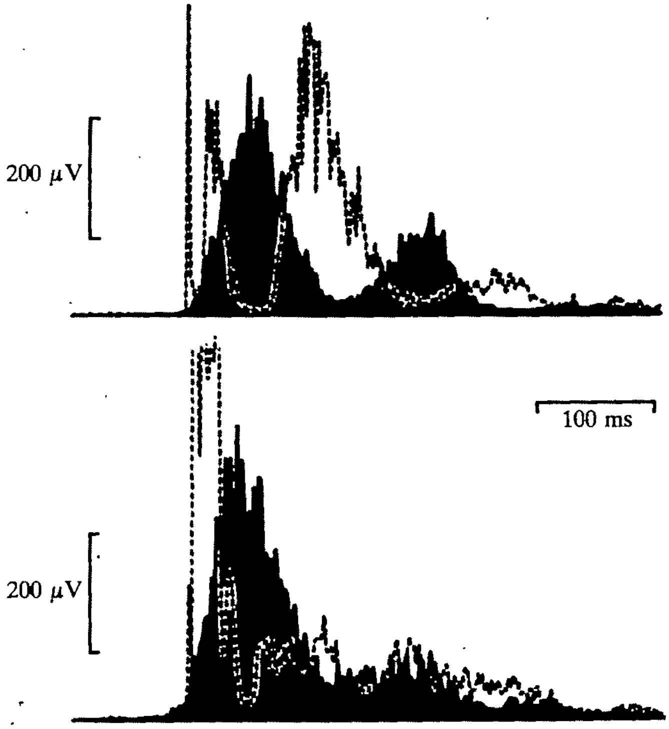

FIG. 4. Comparison of the effect of brain stimulation with peripheral nerve stimulation on a rapid wrist flexion movement in response to an auditory signal at the beginning of the sweep in a single subject. Shown is the average rectified EMG from the agonist wrist flexor muscles. The average control EMGs are shown by solid traces (*top*, n = 23; *bottom*, n = 13). The dotted lines show the average EMG when a stimulus was delivered 100 ms after the auditory tone, before the expected onset of the first agonist burst. The brain was stimulated electrically at 70% intensity (*top trace*, n = 16) and the median nerve was stimulated with 3 supramaximal stimuli separated by 4 ms (*bottom trace*, n = 15). The movement EMG pattern is delayed only when a brain stimulus is given. The peripheral nerve stimulus has the effect of reducing the size of the movement EMG bursts.

segmental sources. For example, changes in muscle afferent feedback following the twitch, activation of Renshaw cells through the antidromic volley in motor axons, and direct stimulation of inhibitory afferents.

The site of delay of voluntary movement

One possible reason for the delay in voluntary movement is that the brain stimulus had rendered the spinal motoneurons refractory by inducing long-lasting inhibition so that they were no longer accessible to a descending motor command. This hypothesis was tested by giving two stimuli (magnetic followed by electric) to the brain during the reaction task. The first stimulus was timed to produce a muscle response at or just before the beginning of the first agonist burst seen in control trials. This stimulus on its own delayed the first agonist burst by some 100 ms (fig. 5). The second stimulus was timed to produce a response in the middle of this delay period. The argument was that if the spinal motoneurons were inaccessible to inputs during the delay period, then a second brain stimulus given at the appropriate time should be incapable of producing a muscle response. In fact, during the reaction task, rather than being inhibited, the muscle response to the second stimulus was larger than when it was given in isolation (size of response to second stimulus as percentage of control in 3 subjects: 115, 139, 377%). Thus it appeared that the delay of voluntary movement caused by a brain stimulus could not be explained by an inhibitory effect at the level of the spinal motoneurons. It appeared that the blocking or delaying of movement had occurred within the brain.

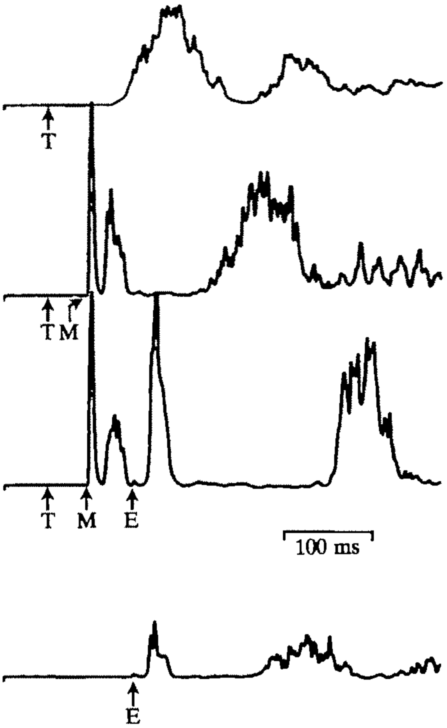

FIG. 5. Testing the spinal motoneuron pool during the delay period. The subject was instructed to flex the wrist as soon as possible after an auditory tone (T). In the *upper trace* the average rectified EMG activity from the agonist wrist flexor muscles during the control movements is shown (average of n = 43). In the *second trace* (n = 11), a 90% intensity magnetic stimulus (M) is given 50 ms after the auditory signal, just before the expected time of onset of movement, and delays the agonist EMG burst by approximately 100 ms. In the *third trace* (n = 11), the same magnetic cortical stimulus (M) is followed after 50 ms by an 80% intensity electrical cortical stimulus (E) which introduces a further delay in the onset of voluntary movement. The *bottom trace* shows the response to the same electrical stimulus (E) given at the same time on its own (n = 10). The response to the electrical stimulus is larger when placed in the delay period than when given in isolation, indicating that the spinal motoneurons innervating these muscles are accessible to descending motor commands during the delay period.

Effect of cortical stimulation on ipsilateral movements

Long delays in movement initiation (> 100 ms) produced by high intensity brain stimulation provided some opportunity for introspection. A common experience during the interval between the tone and movement onset was one of willing the movement but being unable to execute it, as if transiently paralysed. This led to the impression that the delay in movement initiation could not be explained totally by a delay in the intention to move. This was borne out in experiments which compared the reaction times of ipsilateral and contralateral movements.

To study the effect of a brain stimulus on movements performed with the wrist ipsilateral to the stimulated hemisphere subjects were trained to make simultaneous bilateral wrist flexion movements. For this experiment electrical stimuli were applied at random 50 ms after the auditory signal to the left or right hemisphere. The averaged rectified EMGs from the left and right wrist flexors are illustrated for one subject in fig. 6. The onset of the left and right agonist bursts was simultaneous in control trials. When an electrical stimulus was delivered to one hemisphere this was no longer the case; the wrist flexor activity in the arm contralateral to the stimulated hemisphere clearly was delayed, whereas that in the ipsilateral arm appeared to be little affected.

This experiment was performed on 11 occasions using 5 subjects. The electrical stimulation intensity varied from 55 to 82% across all experiments. Although an attempt was made to stimulate one hemisphere exclusively, it is worth noting that in most of these experiments a small direct muscle response could sometimes be seen in the ipsilateral forearm muscle. The reaction time was measured

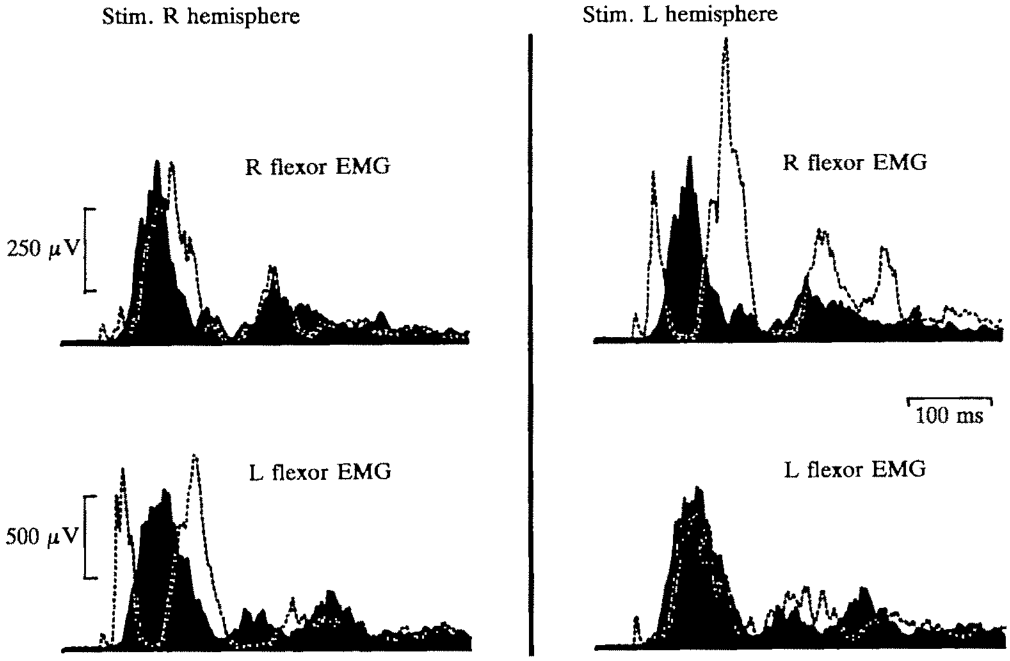

FIG. 6. Effect of unilateral cortical stimulation on bilateral wrist flexion movements in response to an auditory signal at the beginning of the trace in a single subject. Shown are the average rectified EMG from the right flexor (*upper traces*) and left flexor (*lower traces*) muscles. Control trials (n = 24) are denoted by solid traces and those trials in which a 60% electrical stimulus was given 50 ms after the audio tone (n = 13) are shown by the dotted lines. Stimuli were applied either over the right hemisphere (*left panel*) or over the left hemisphere (*right panel*). In control trials the onset of the first agonist EMG bursts are simultaneous in both arms. With a cortical stimulus, movement of the contralateral arm is delayed considerably more than movement of the ipsilateral arm. (Note the small direct muscle response which follows the stimulus artefact in the ipsilateral arm.) The relatively small delay of ipsilateral movements indicates that the subject's time of intention to move is barely affected by the cortical stimulus.

in individual trials and mean values were calculated for each arm both for control trials and trials in which an ipsilateral/contralateral brain stimulus was given. In control trials the mean reaction time was 93±5 ms (mean ± SEM). With a brain stimulus the contralateral reaction time increased to 151±9 ms (paired t test: $t = 9.76$, $df = 21$, $P < 0.001$) while the ipsilateral reaction time increased to only 107±6 ms ($t = 6.69$, $df = 21$, $P < 0.001$). Even though the ipsilateral reaction time was altered by the brain stimulus the delay was small compared with that of the contralateral arm (ipsilateral: 15±2 ms; contralateral 58±6 ms; $t = 7.07$, $df = 21$, $P < 0.001$). Processes other than perception of the auditory stimulus or the intention to move must have been affected to account for the reaction time differences between the two arms.

Effect of changing the interval between auditory and cortical stimuli

This experiment was performed in 3 subjects, using magnetic stimulation applied laterally to only one side of the head. In all subjects the major effect was on the reaction time of the arm contralateral to the stimulating coil. Fig. 7 shows that as the interval between auditory reaction signal and brain stimulation was lengthened, the reaction time was increasingly prolonged. Thus if stimuli were given at the same time as the auditory signal, there was only a small effect on reaction time. If the same stimuli were given 60 ms after the auditory signal, and therefore closer to the expected onset of movement, then the effect was more pronounced. The slope of the regression line relating time of stimulus to reaction time was 1.1±0.4 ($P < 0.02$).

Fig. 7 also shows that the brain stimulus had a small effect on voluntary reactions in the ipsilateral arm despite the lack of any detectable direct EMG

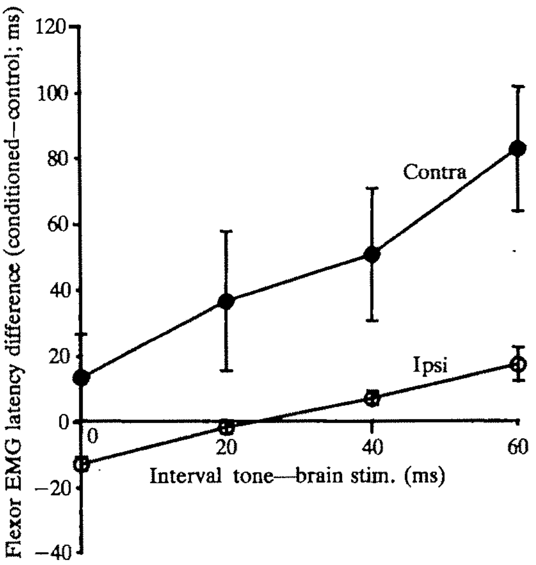

FIG. 7. Effect of unilateral magnetic stimuli to the brain given at different times after the auditory reaction signal to move, on the delay of the first agonist EMG burst in the contralateral (*filled circles*) and ipsilateral (*open circles*) wrist flexor muscles. The latency to the onset of the first agonist burst in control runs was subtracted from that in runs prefaced by the magnetic stimulus to give the delay induced by the latter. Shown is the mean (±SEM) data taken from 3 subjects.

responses on that side in the majority of trials. However, the effect was different to that on the contralateral side in two ways. First, voluntary responses on the contralateral side were delayed at all timings of the cortical shock. In 2 of the 3 subjects, ipsilateral reaction times were shortened by a brain shock given at the same time as the auditory reaction signal. Secondly, the slope of the regression line relating timing of the brain stimulus to reaction time (0.5 ± 0.1, $P < 0.001$) was only half that on the contralateral side. This difference was borne out by the presence of a significant interaction term in the ANOVA between these sets of data (F (3,6) = 8.8, $P < 0.05$).

Effect of cortical stimulation on the antagonist burst

In a final series of experiments we were interested to know if a brain stimulus given after the onset of movement could delay the first antagonist burst without affecting the timing of the agonist. This experiment was performed in 4 subjects. They were instructed to perform unilateral wrist flexion movements in response to an auditory stimulus. Magnetic stimuli were given with the coil centred on the vertex and the stimulus was timed to produce a direct muscle response at the onset

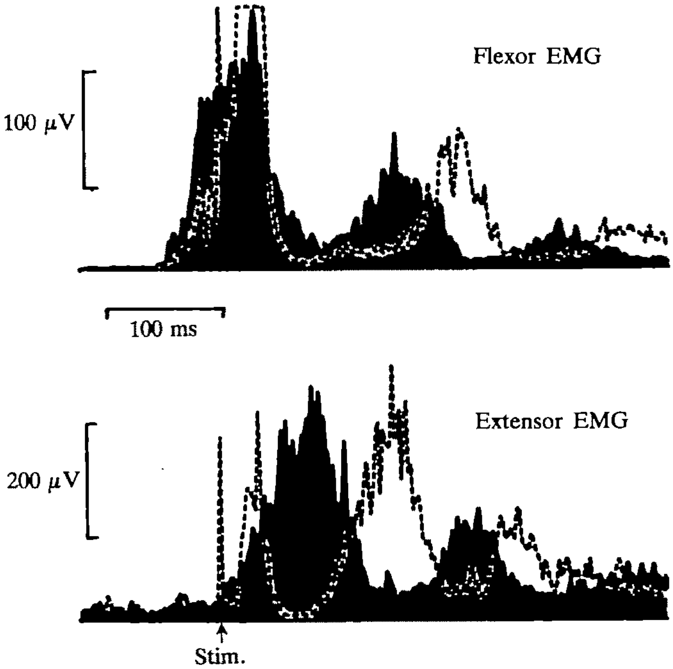

FIG. 8. Effect of giving a 65% magnetic cortical stimulus 120 ms after the auditory signal (which occurred at the beginning of the trace), during the occurrence of the first agonist EMG burst associated with a rapid wrist flexion movement in a single subject. Shown is the average rectified EMG from the agonist wrist flexor muscles (*upper traces*) and the antagonist wrist extensor muscles (*lower traces*). The average of the control trials (n = 24) is shown by the solid traces and those trials in which a cortical stimulus was given (n = 10) by the dotted lines. Although the cortical stimulus was given too late to affect the timing of the first agonist EMG burst, the first antagonist (and later) burst is delayed by the stimulus.

of the first antagonist burst. Under this condition the onset of the first antagonist burst (and later bursts) was delayed although the stimulus was given too late to affect the latency of the first agonist burst. An example from one subject is illustrated in fig. 8.

DISCUSSION

The present results show that an appropriately timed stimulus to the brain can delay the onset of a voluntary reaction without affecting the form of the response. The experiments using double brain stimuli indicate that the spinal cord is relatively accessible to descending inputs during the period of the delay. Thus the effect is unlikely to be due to refractoriness of spinal cord mechanisms, and is probably caused by interference with some mechanism within the brain.

It is not surprising that a stimulus to the brain can cause inhibition as well as excitation. There have been many previous observations in man made during the course of neurosurgical operations showing that repetitive electrical stimuli applied directly to motor cortex (or supplementary motor area) can inhibit ongoing voluntary movement (Penfield and Jasper, 1954). Such stimuli often induce a sensation of paralysis in conscious subjects as well as producing muscle twitches in contralateral body muscles. More recently, the new transcranial techniques have been used to demonstrate that stimuli given over occipital regions can inhibit perception of a transient visual stimulus (Amassian *et al.*, 1988). The novel feature of the present results is that although voluntary reaction is suppressed for a short time, it is not abolished but delayed. The delay does not seem to be due to some general effect of the brain shock on perception of the auditory 'go' signal, nor on the intention of the subject to respond to the signal. Stimuli given to one side of the scalp had a much greater effect on reactions in the contralateral arm.

Why then is the voluntary reaction delayed? There are three possible explanations. (1) The shock might produce slowing of transmission through a central process, thereby delaying the final motor outcome. However, there is no evidence that a neural signal can be slowed to such an extent as to produce delays of the order of 50–100% in total reaction time. (2) The shock may destroy part of the 'program' of movement which would then have to be recalculated before the final reaction can be expressed. If we imagine that part of this program is calculated in the period after the reaction signal, then this could account for the increased delay when the shock is given late. More of the program could be destroyed the closer the shock was delivered to the onset of movement. Similarly, large shocks would disrupt the program more than small shocks. However, this explanation suffers from the difficulty that the brain would have to identify which part of this program had been disrupted and then recalculate the appropriate segment.

The final explanation seems the most likely. That is that the stimulus might halt transmission of information through a central process, perhaps by inhibiting a group of strategically placed neurons. These cells would be unresponsive until they had recovered from the inhibitory process and hence the movement would be delayed. The more intense the stimulation, the longer the period of inhibition and the greater the delay in movement.

If the delay in voluntary movement is caused by inhibition of certain neurons, then we may ask where in the brain are these cells located, and at what stage in the evolution of a movement are they normally recruited? Since the greatest effect was seen when the stimuli were applied over central areas of scalp contralateral to the moving arm, it seems likely that the block occurs within the motor or adjacent areas of cortex. This would be consistent with the finding that delays were rarely observed unless the shock had also produced a direct cortically-mediated EMG response in the muscle. However, the observation that small delays sometimes could be seen in ipsilateral muscles without any direct EMG response suggests that minor delays can occur through stimulation of other areas of brain.

The cells which are inhibited by the shock probably are recruited late within a voluntary reaction. Maximum delay always occurred when the brain shock was given close to the expected start of the movement. The amount of delay was linearly related (with a slope of 1) to the timing of the shock within the reaction period. This could be explained by supposing that the shock inhibits susceptible neurons for a given amount of time no matter when the shock is given. According to this scheme, the natural flow of movement signals within the brain would only be affected if the stimulus were applied within certain time constraints. Thus if the neurons are inhibited for, say, 50 ms and the shock is given 50 ms before the time at which they are activated in a normal movement, then no delay will be apparent. If the shock is given 50 ms later, at the time when they are normally active, a delay of 50 ms will be evident. Within these limits, proportional effects would be seen.

The finding that a stimulus to the brain can delay a voluntary movement without changing its form has important implications for theories of central control of movement. Since the movement eventually was executed in an intact form, the movement commands upstream from the blocked site must have been retained for the duration of the block. The implication is that the motor commands were held in some form of short-term memory store which allowed them to continue unabated as soon as the inhibited neurons had recovered. The concept of a short-term motor store has been used previously, for example, to explain why the simple reaction time may be shorter than the choice reaction time. When the subject knows in advance what movement is to be performed in response to a reaction signal (simple reaction task), he is able to prepare the movement and hold it in a buffer store until the reaction signal is perceived. This would give some time advantage since the initial preparatory stages would have been performed in advance and would not need to be repeated. In a choice reaction task, however, this would not be possible because the impending movement task would not be known until the reaction stimulus was given.

If motor instructions are stored in a temporary buffer, then the ability to delay performance of movement has one further implication. Some form of internal monitoring system must exist which, depending on the precise cause of the delay, might, for example, check the progress of the motor instructions (e.g., by internal reafference), or check the integrity of the stored program, or check the readiness of the downstream sites to respond to the impending instructions. Whatever the mechanism, the brain must compensate for the fact that the delivery of the program for the intended movement has been disrupted or that it has failed to be executed at the appropriate time. Without internal feedback the brain would have no early knowledge of its failure to deliver the motor commands at the intended time. Inspection of afferent signals from the periphery could provide this knowledge. If this were the case, however, there would be a lag before a new set of instructions were issued because of the time taken for signals to travel between the brain and the periphery. The small delays in movement onset produced by low-intensity stimulation argues against the possibility of feedback from the periphery being responsible. It seems more likely that this information is gained by monitoring the motor command signals by some form of internal reafference.

The finding that the antagonist burst could be selectively delayed by a cortical stimulus given at the end of the agonist burst bears on the issue of its origin. The function of the antagonist burst is thought to act as a brake to decelerate the moving limb in order that it stops at the intended end position (Marsden *et al.*, 1983). One unresolved question is whether the antagonist burst is organized centrally or is simply a stretch reflex arising from stretch of the antagonist muscle during agonist shortening. Since the timing of the antagonist burst could be selectively delayed and was therefore independent of the agonist burst timing, the stretch reflex hypothesis does not hold. Our results support the concept that the antagonist burst is centrally organized in advance of the movement. This interpretation agrees with the results of experiments performed on deafferented human subjects (Hallett *et al.*, 1975; Rothwell *et al.*, 1982). These studies show that the first agonist and antagonist bursts are structured normally in the deafferented patients and provide strong evidence for a central organization of the bursts. These experiments, however, could not distinguish between whether the antagonist burst was organized independently in the brain or represented part of a complex response of the spinal machinery to a simple descending input. We suggest that our results place the site of organization of the antagonist burst within the brain. We presume that the stored motor instructions contain information both about the agonist and the antagonist muscle activities which govern the intended movement. Thus, even if the onset of the stimulus-induced block occurred after the agonist burst information had passed through, the block was still capable of delaying the onset of later centrally organized movement commands to the antagonist muscle.

In conclusion, the phenomenon of delaying movement by a brain stimulus provides some insight into central mechanisms which control movement during a simple reaction task. We suggest that the initial sequence of agonist/antagonist muscle activities are coded and stored within the brain in a motor memory, probably somewhere else than in the motor cortex. Movement occurs upon sequential release of these coded instructions to the motor cortex. The running of this motor program can be interrupted at any time by an appropriately timed cortical brain stimulus. When the effect of the stimulus has worn off, then the program continues running from where it left off, possibly under feedback control from an internal monitoring system.

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TRANSIENT PARESIS IN MYOTONIC SYNDROMES

A SURFACE EMG STUDY

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SUMMARY

In order to study transient paresis, force and surface electromyograms (EMG) were recorded from the biceps brachii in 3 patients with recessive myotonia congenita, in 8 with myotonic dystrophy and in 3 controls. Epochs of 0.34 s EMG signal were stored every 0.44 s and processed to determine the integrated EMG (IEMG), the power spectrum and the average muscle fibre conduction velocity (MFCV). The protocol consisted of 5 maximal voluntary contractions lasting 10.3 s and 13 s recovery.

During the first 1–1.5 s the MFCV and median frequency (Fmed) of the power spectra of the controls increased (mean increase 12.5% and 14%, respectively) in all 5 consecutive contractions. Subsequently, MFCV, Fmed and force declined as a consequence of fatigue. Both the initial force and MFCV declined with successive contractions. The results in myotonic dystrophy were not different from the controls, except that the changes during fatigue were far less pronounced.

These events are the reverse of the changes found in myotonia congenita in which an initial loss of force (maximal by 61–79%) and a decline of the IEMG (maximal by 79–92%) was found during the first contraction. This transient paresis was accompanied by a dramatic fall in the MFCV concomitant with a shift of the power spectrum to the lower frequencies. The first MFCV measurement of the 5 contractions was always normal. The decline in MFCV was maximal after 1.5–2.5 s and varied for the 3 patients from 32–52%. In general, the decline in force, IEMG and MFCV lessened with each successive contraction (warming-up phenomenon), though sudden deteriorations were sometimes observed during later contractions. The same results were found for brachioradialis and abductor digiti minimi.

The results provide evidence that transient paresis is of clinical relevance in myotonia congenita and that it is caused by alterations in the muscle membrane. These membrane changes result in a strong decline of the muscle action potential conduction velocity and consequent depolarization block of the muscle fibres. Our method did not show the presence of transient paresis during voluntary contraction in myotonic dystrophy.

INTRODUCTION

In several myotonic syndromes, especially myotonia congenita and paramyotonia congenita and to a lesser degree in myotonic dystrophy, transient paresis after

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physical rest has been described. After an initial normal or near-normal force a fast temporary decline in strength is noted. Repetitive contractions result in a decline of this 'transient paresis', the warming-up phenomenon. Clinical investigations have included mechanographic studies combined with EMG measurements (Burke *et al.*, 1974; Ricker *et al.*, 1978). The decline in compound muscle action potentials (CMAPs) during repetitive nerve stimulation has most often been used to investigate transient paresis (Ricker and Meinck, 1972; Ricker *et al.*, 1973; Brown, 1974; Aminoff *et al.*, 1977; Streib *et al.*, 1982; Wagner and Zett, 1982; Rossi *et al.*, 1985; Gutmann *et al.*, 1986). The EMG studies were limited to amplitude measurements. The amount of electrical energy in the EMG signal is an indication of the number of active fibres. However, a decline in EMG can have different explanations which cannot be traced by means of this approach. In myasthenia gravis, for example, a decline in CMAP during repetitive nerve stimulation is the result of disturbed neuromuscular transmission.

The cause of transient paresis in myotonia congenita is thought to originate in the muscle membrane, since the decline in CMAP did not improve with anticholinesterase inhibitors (Ricker *et al.*, 1973) and direct electrical stimulation of the muscle (Brown, 1974) also showed a reduction in CMAP. On the other hand, Wiles and Edwards (1977) postulated a change in the contractile apparatus of the muscle as a contributory factor for the force loss, since the changes in EMG energy content were found to be too small to explain the loss in force.

The clinical relevance of transient paresis is not yet well defined. In general, for myotonic dystrophy it is not even mentioned as a clinical sign or symptom. It is well known that in patients with myotonia congenita their movements can 'freeze'. In all major handbooks this is interpreted as a consequence of stiffening due to a bout of generalized myotonia (e.g., Lipicky, 1979; Harper, 1986). In some publications, on the other hand, it is stated that the inability to move is due to transient paresis (Ricker *et al.*, 1973; Streib *et al.*, 1982).

Determination of muscle fibre conduction velocity (MFCV) promises to be an important neurophysiological tool in studying abnormal muscle membrane function (Zwarts *et al.*, 1988). Surface EMG was therefore processed to determine the average MFCV, the power spectrum and the integrated EMG (IEMG) to study the cause and significance of transient paresis in the myotonic syndrome. This was combined with measurements of force during repeated maximal isometric contractions.

SUBJECTS AND METHODS

Three patients with autosomal recessive myotonia congenita, 8 with myotonic dystrophy and 3 healthy male controls were studied after informed consent had been obtained. The 3 controls were aged 29, 33 and 35 yrs.

The mean age of the 8 patients with myotonic dystrophy was 45.6 yrs (range 23–64 yrs). The diagnosis was established by the clinical features, the presence of cataract by slit lamp investigation and myotonia runs on needle EMG. Except for one mother and daughter, the patients were unrelated.

The 3 patients with myotonia congenita were male, aged 23, 31 and 40 yrs, respectively. All complained of difficulty in movement due to fluctuations in strength, especially when sudden movements were necessary after rest. Cold weather did not influence the complaints. The diagnosis was based on the presence of muscle hypertrophy and the EMG finding of myotonia in the absence of myopathic changes. Slit lamp investigation of the eyes was negative. Recessive inheritance was likely. The parents of the 3 patients were found to be normal on neurological and needle EMG examination. In 1 patient a sibling was affected.

Force measurements

Isometric force for elbow flexion was measured at the wrist with a strain gauge. The arm was maintained in a horizontal position, supported and fixated at the elbow. The elbow was in a semiflexed position, the lower arm making an angle of 120° with the upper arm. The exerted force was displayed in front of the subject on a voltmeter and written on a paper recorder (*see also* Zwarts *et al.*, 1987*a*). For measurements on the brachioradialis the arm was in a pronated position. The force of the abductor digiti minimi was measured with a strain gauge with both the hand and digits 1-4 fixed and the force of isometric abduction of the fifth finger measured at the second interphalangeal joint.

EMG recording

A longitudinal array of 3 electrodes was used, the distance between the electrode centres being 10 mm. The diameter of the electrodes was 2 mm. The centre electrode was used as a common electrode for the two EMG signals. The skin was cleaned with alcohol and lightly abraded, but no electrode paste was used. Care was taken to place the electrodes parallel to the direction of the muscle fibres between the motor point and the tendon. Finding the optimum position for the electrode was facilitated by a real-time estimation of the cross-correlation coefficient and the MFCV measured over a quarter of the signal and by a graphic display of the digitized signals.

Data analysis

The two EMG signals were differentially amplified (Disa EMG amplifier, type 14C13, bandpass 20-20000 Hz) and digitized by a 12-bit A/D converter with a sample rate of 6024 Hz over a signal period of 0.34 s. Since the changes of the EMG signal of the patients with myotonia congenita were found to take place within seconds, it was necessary to make a fast repetition of the measurements possible by storing the data on a Winchester hard disc. In this way, epochs of 0.34 s of signal could be measured and stored every 0.44 s. The data were analysed by a PDP 11/23 computer. The power density spectrum was computed over the frequency range of 5-250 Hz by applying the fast Fourier transform to the digitized signal. The frequency resolution was 0.5 Hz. After applying the Papoulis window for spectral smoothing this was reduced to 5.0 Hz. The median frequency was calculated from the spectra obtained and used to summarize the changes in frequency of the EMG signal. In addition, the integrated EMG (mean rectified value of the EMG signal) was used as a measure of EMG activity. These variables are derived from Hermens *et al.* (1984). The conduction velocity was calculated after interpolation—which raises the sample frequency to 12048 Hz—by the cross-correlation method (Naeije and Zorn, 1983; Sollie *et al.*, 1985). MFCV measurement with a cross-correlation coefficient of less than 0.75 was not accepted.

The relation between variables was studied with linear regression analysis. The significance of the difference between two means was determined by two-tailed Student's t test.

Procedure

The experiments were performed after 10 min rest of the arm. The subjects were exhorted to sustain a maximal flexion of the forearm during 10.3 s. This was ordered by a verbal command and at the same moment the measurements were initiated by a foot switch. This was repeated 5 times with 13 s recovery between the contractions. In 2 patients with myotonia congenita the procedure was repeated with measurements of the brachioradialis and the abductor digiti minimi in order to study the extent of the abnormalities. The brachioradialis was chosen since this muscle permits accurate MFCV estimates; the abductor digiti minimi was chosen as a distal muscle. The EMG recordings of the latter muscle were not analysed with respect to the MFCV estimate, because the distance between the motor point and the tendon is too small to permit application of this method.

RESULTS

Controls

The mean values for MFCV, Fmed, force and IEMG are shown in figs 1 and 2. The trends were similar for all controls. The values of the second and fourth contractions were intermediate between the foregoing and next contractions and have been left out for clarity. During the contractions two phases could be distinguished. At the start of the contraction, the MFCV rose (mean: 12.5%) and the power spectrum shifted to the higher frequencies as can be seen from the increase (mean: 14%) in median frequency (Fmed). The course of both variables was identical for every contraction despite a lowering of the initial value due to fatigue (*see also* fig. 3). The second (fatiguing) phase was characterized by a slight decline in force, but the IEMG changed little. In contrast, MFCV and Fmed both declined from the initial values: the mean values of the decay during the first contraction were 13 and 32%, respectively, for the last contraction 18 and 42%.

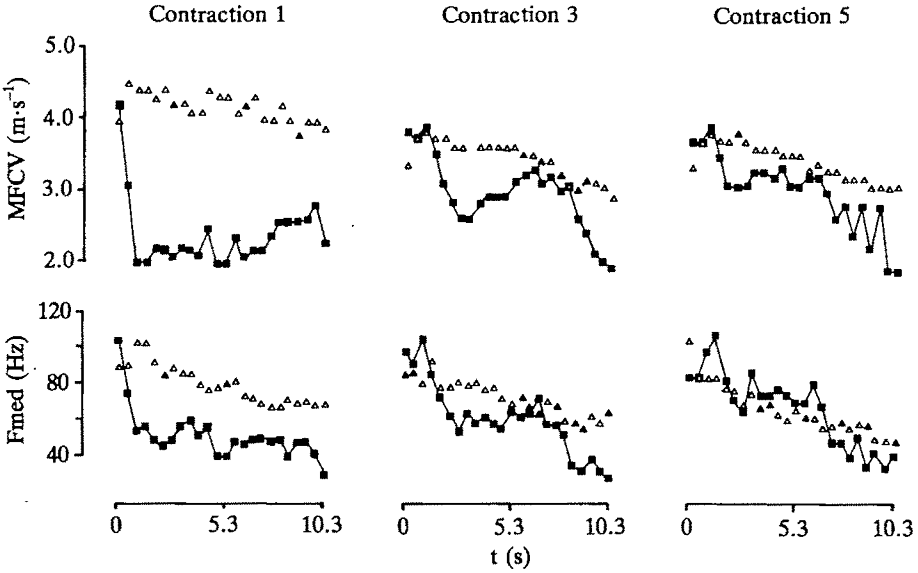

FIG. 1. Change in muscle fibre conduction velocity (MFCV) and median frequency (Fmed) of the power spectrum of surface EMG of biceps brachii. Triangles = mean results for 3 controls; closed squares = measurements for myotonia congenita *Case 3*.

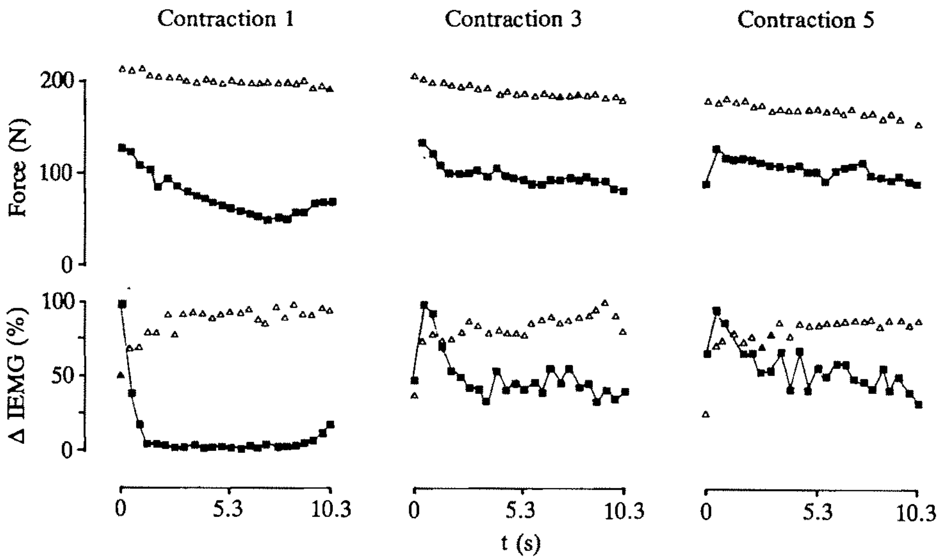

FIG. 2. Force and integrated EMG (IEMG) changes for the same measurements as in fig. 1. The symbols have the same meaning.

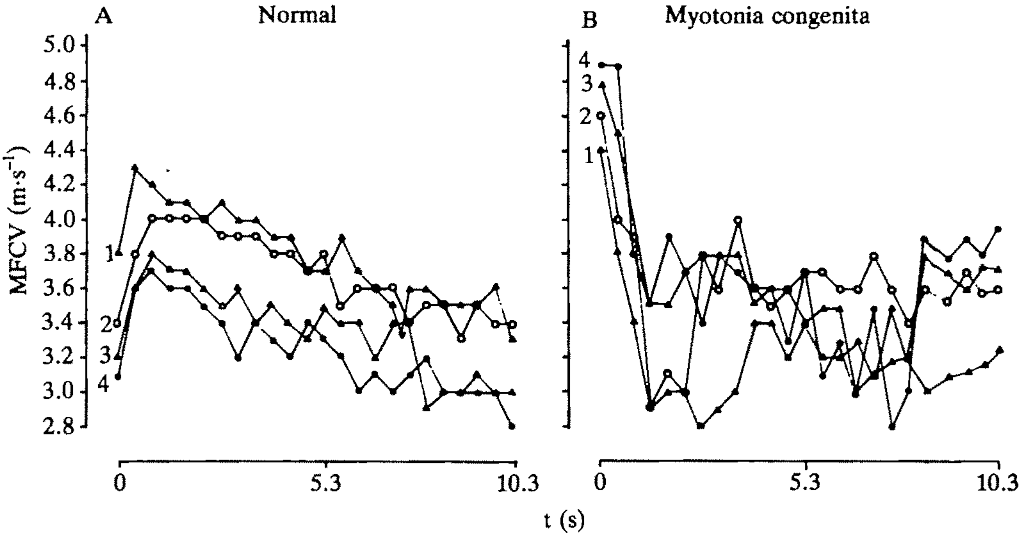

FIG. 3. Muscle fibre conduction velocity (MFCV) changes during the first 4 contractions of a control (A) and a myotonia congenita patient (B). Note the difference in course and the higher initial values of the MFCV of the patient.

Myotonic dystrophy

The changes during the first phase were similar to those of the controls. The initial value of the maximal voluntary contraction was much lower in the patients (mean value for the controls: 210 N; for the patients: 84 N). The changes of the

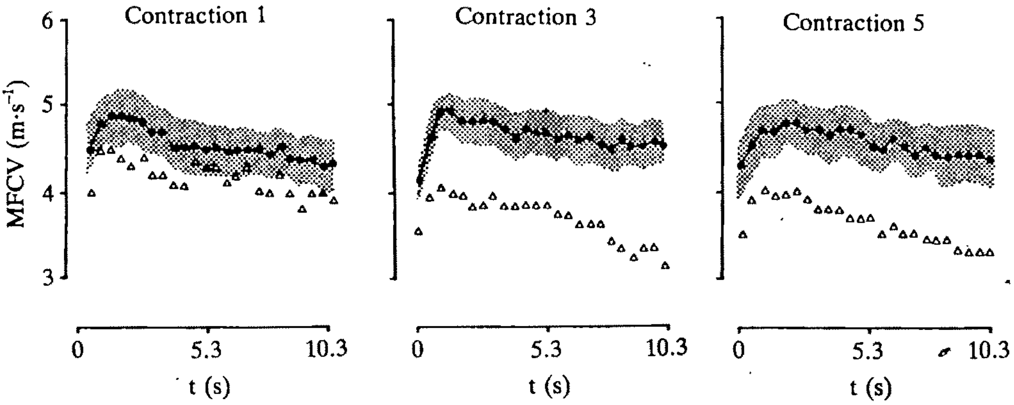

FIG. 4. Mean muscle fibre conduction velocity (the shaded area is ±SEM) for the 8 myotonic dystrophy patients (filled symbols); the triangles are the means for the controls.

MFCV and Fmed during the second phase were less pronounced than the control values: the mean values of decay of the first contraction was 11 and 23%, respectively, of the last contraction 8.5 and 15% (*see* fig. 4). The decrease of the initial values of the MFCV and Fmed during the successive contractions was not present in the patients.

Myotonia congenita

The changes were the reverse of the changes found in the controls. The decline of the first contractions of the patients is given in the Table. Representative data from Case 3 for biceps brachii are plotted in figs 1 and 2 to illustrate the time

TABLE. MAXIMAL DECLINE OF EMG AND FORCE OF THE 3 MYOTONIA CONGENITA PATIENTS DURING THE FIRST CONTRACTION (PERCENTAGE VALUES)

	EMG			
Case (age, yrs)	*Conduction velocity*	*Median frequency*	*Integrated EMG*	*Force*
Biceps brachii				
1 (23)	33	21	79	63
2 (31)	23	43	92	79
3 (40)	52	45	92	61
Brachioradialis				
2	56	62	84	83
3	54	53	93	77
Abductor digiti minimi				
2	*	72	80	71
3	*	64	77	78

* Not measurable on this muscle by the method used.

course of transient paresis and recovery (the warming-up phenomenon). During the first contractions a sharp decline in MFCV, Fmed and IEMG occurred. The change in force was generally slower. After this decline there was no tendency for recovery. The abnormalities lessened with consecutive contractions and an improvement in the variables was sometimes seen during the contraction (*see* the MFCV and Fmed in the third contraction in fig. 1), although at the end of the contraction a deterioration could occur (contractions 3 and 5 in fig. 1). At every new contraction after rest the EMG variables started with the initial values.

Fig. 3 shows the changes in MFCV of Case 2 as compared with a control. The initial rise in MFCV of the controls was absent in all myotonia congenita patients. The mean initial value ($\pm$SD) of the MFCV of the patients was 4.6 ± 0.3 m.s^{-1}; for the controls this was 4.0 ± 0.2 m.s^{-1}, which is significantly lower (Student's t test, $P = 0.045$).

An example of the two EMG signals during the course of the second contraction is given in fig. 5, together with the calculated values. The signals displayed are a quarter of the epochs of 0.33 s on which the values were calculated. Both EMG

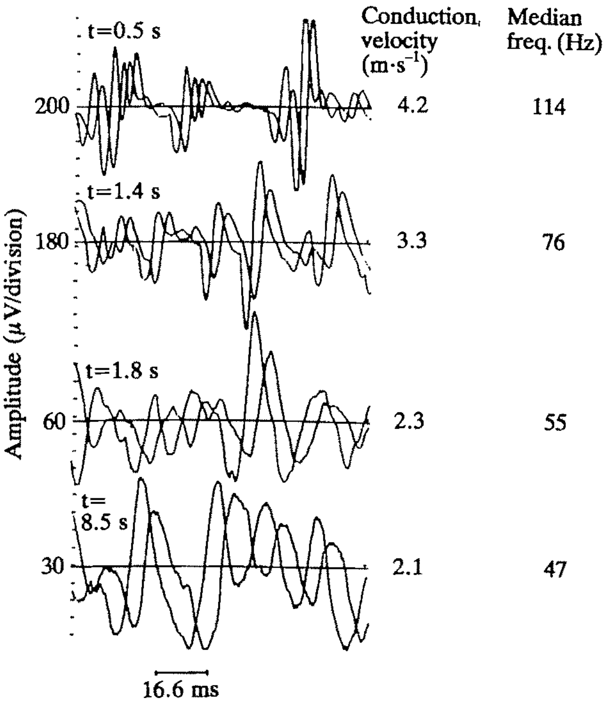

FIG. 5. Examples of the digitized EMG signals of the second contraction of the brachioradialis of myotonia congenita *Case 1*. The signals displayed are a quarter of an epoch. The time of registration from the beginning of the contraction is indicated by t in the upper left corner of the graphs. The sharp decline in amplitude can be seen from the change in calibration of the ordinate. For every measurement the MFCV and Fmed calculated are also given.

signals are very similar, indicating high cross-correlation values, in general between 0.9 and 1. The values of the second measurement, at t = 0.5 s, are normal. The following two measurements show the fast decline in IEMG, Fmed and MFCV (as can be seen from the increasing delay between the 2 signals). The last measurement demonstrates the absence of restoration during the contraction. The EMG signal of Case 2 declined sometimes in such a way that no reliable MFCV estimates could be made, which was evident from the low cross-correlation coefficients.

In some measurements, especially during the second and third contraction, large fluctuations of the variables could occur within seconds. Fig. 6 gives an example of the second measurement of the brachioradialis of Case 2. Sometimes these fast changes were also observed within one epoch of 0.33 s (fig. 7).

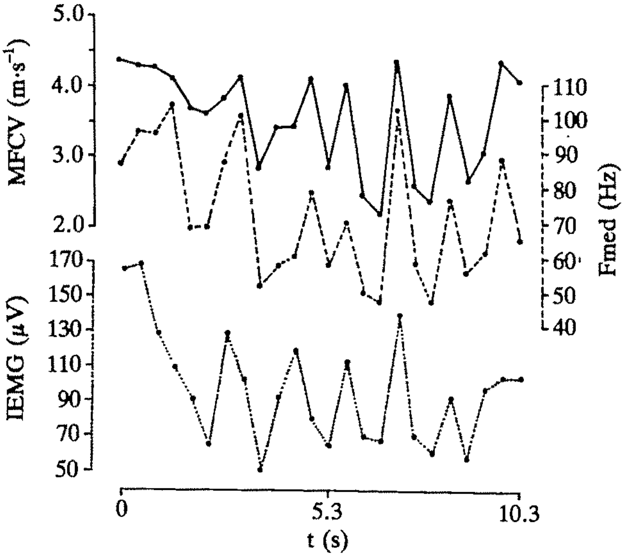

FIG. 6. Example of the fast changes of the EMG signals during the second contraction of myotonia congenita *Case 2*.

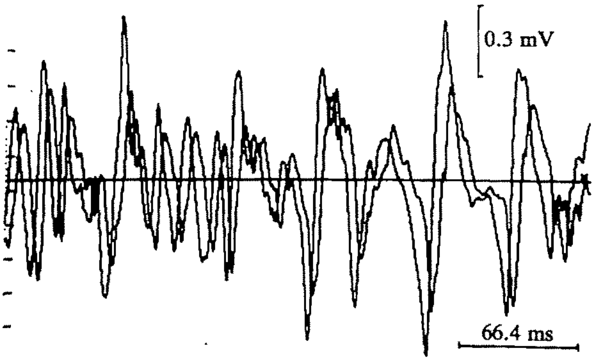

FIG. 7. EMG signals of one measurement of myotonia congenita *Case 2* showing the fast change in conduction velocity during one measurement.

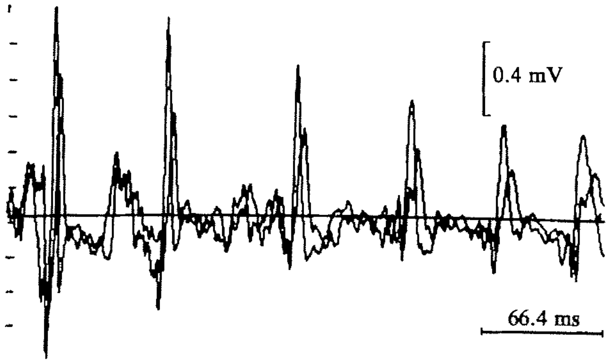

FIG. 8. Recurrence of a motor unit potential in the course of the second contraction of the brachioradialis of myotonia congenita *Case 3*. Note the fast decline in amplitude; the increasing delay between the two motor unit signals indicates the decrease in muscle fibre conduction velocity.

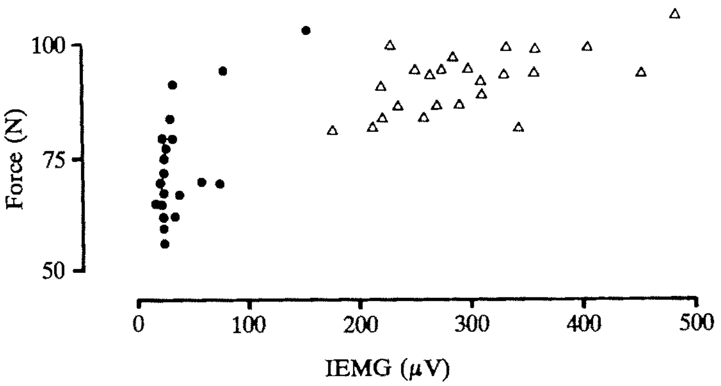

FIG. 9. Relationship between force and IEMG of the first and last contractions of myotonia congenita *Case 1*. Note the linear relationship during the last contraction and the curvilinear relationship in the first contraction with a higher position; this indicates that the force decline is less than the decrease of IEMG. The time course of the changes during the first contraction is down from right to left. Closed circles = contraction 1; open triangles = contraction 5.

A significantly linear relation was found between the MFCV and Fmed of the power spectrum. The mean slope of the least-square fits of the first and last contractions of the 3 patients was 31.6 ± 8.7, the mean correlation coefficient was 0.79 ± 0.16 (P values ranged from 0.02 to 0.0001). The same values of the 3 controls were 47.2 ± 10.7, mean r = 0.84 ± 0.06 (the P values were significant except for one contraction).

Generally, force and IEMG changed simultaneously in the myotonia congenita patients, but the change in force was usually less than the decline in IEMG (*see also* Table). This was especially true for the first contractions, resulting in a nonlinear relationship (*see* fig. 9).

DISCUSSION

Transient paresis has been described as an abnormal decline in force. It is most pronounced after physical rest and disappears after successive contractions, which is generally referred to as 'warming-up'. This phenomenon is confined to the myotonic syndromes and is described in recessive generalized myotonia congenita (Becker type), dominant myotonia congenita (Thomson's disease), paramyotonia congenita, hyperkalaemic periodic paralysis and myotonic dystrophy. Although the hallmark is loss of force, in most studies the decline of the CMAP during repetitive nerve stimulation is used to demonstrate its presence (*see* Introduction). In order to investigate the muscle membrane changes during voluntary contraction, new techniques to analyse the surface EMG have been used. Thereby it was possible to study important properties of muscle membrane function (such as the average action potential conduction velocity) during voluntary contraction at all force levels in addition to the energy content of the signal. By measuring epochs of 0.33 s signal every 0.44 s it was possible to analyse the fast changes at the start of the contraction. Closely related to the average MFCV is the frequency content of the EMG signal (for a review, *see* Lindström and Petersén, 1983, and De Luca, 1984). In general, a linear relationship has been found between the change in MFCV and the change of the power spectrum as determined by the change in median or mean frequency. This relationship has been studied mainly during fatiguing contractions (Naeije and Zorn, 1982; Sadoyama *et al.*, 1983; Arendt-Nielsen and Mills, 1985; Zwarts *et al.*, 1987*a*), and was also demonstrated in periodic hypokalaemic paralysis (Zwarts *et al.*, 1988). Intuitively, this relationship can be understood by imagining the muscle fibre action potential to travel along the surface electrodes; the time course of the potential changes—and therefore the frequency content of the signal—is then related in a linear way to the velocity of the action potential.

Controls

In the controls (and the myotonic dystrophy patients) the MFCV shows an initial increase. This can be explained by the higher conduction velocities of the fast-twitch motor units (Hopf *et al.*, 1974; Andreassen and Arendt-Nielsen, 1987; Sadoyama and Masuda, 1987; Zwarts *et al.*, 1988), which are known to be recruited later (Henneman *et al.*, 1965).

The decline of MFCV, Fmed and force after the initial increase in MFCV is well known from fatigue studies in normals. The IEMG rises in submaximal static contractions, but declines in maximal contractions, possibly due to a decline in firing rate of the motor neurons during fatigue (De Luca, 1984). During the 10.3 s of contraction in our study the IEMG increased, this was also found by Milner-Brown *et al.* (1986). Interestingly, after each rest period, the initial value of the MFCV of the controls also declines. As argued above, this initial value of the MFCV mainly originates from type I (or slow) muscle fibres. These fibres are said to be fatigue-resistant (Burke *et al.*, 1973), but the clear decline of the MFCV seems in contradiction with this notion. An important difference between the physiological experiments mentioned and our protocol is the fact that during maximal static contractions the muscle can be regarded as working in anaerobic conditions, while the biochemistry of type I fibres is tuned to aerobic conditions. This agrees with the findings of Sahlin *et al.* (1987). They concluded that the soleus of the rat, a muscle mostly composed of type I fibres, cannot be termed fatigue-resistant under anaerobic conditions since the decrease of isometric twitch tension did not differ from fast-twitch motor units.

Myotonic dystrophy

The less pronounced changes of the EMG variables of the myotonic dystrophy patients can be explained by the much lower force level as compared with the controls. It is known that the contracting force level influences the endurance time to a high degree (Rohmert, 1960). The point at which the blood flow is occluded is known to be determined by the absolute force level (Barnes, 1980).

Contrary to our expectations, none of the myotonic dystrophy cases showed signs of a transient paresis. On the other hand this result is in agreement with the lack of clinical descriptions of transient paresis in this disorder. The reason for this apparent discrepancy may lie in the different techniques used. First, our study was focused on muscles which offer the opportunity of measuring the MFCV. Since the studies with repetitive nerve stimulation invariably used distal muscles and since in myotonic dystrophy these are predominantly affected, this could account for the differences. Even so, preliminary studies on abductor digiti minimi in 2 patients with myotonic dystrophy were normal. Secondly, transient paresis in patients with this disorder could only be elicited with higher stimulation frequencies and with longer intervals after the beginning of the stimulation compared with myotonia congenita patients (Aminoff *et al.*, 1977), although these stimulation frequencies (10–15 Hz) lie well within the normal frequencies of the motor neurons during maximal contraction.

Myotonia congenita

The initial rise in MFCV was completely absent in the myotonia congenita patients. Since no central disturbances are recognized in this disorder, we assume that the 'size principle', that is, the orderly recruitment of motor units, is present in myotonia congenita. The explanation may be found in the histological abnormalities of the muscle. An abnormal hypertrophy of the muscle fibres was found by Crews *et al.* (1976). In addition, it was shown that the frequency peak in fibre diameters was unimodal in myotonia congenita (Kuhn *et al.*, 1979). Assuming that the MFCV is related to fibre diameter (Håkansson, 1956), these histological findings can explain both the lack in initial rise (because of the unimodal frequency spectrum of the diameters) and the higher initial value due to fibre hypertrophy. Of course it cannot be excluded that alterations in the membrane properties are also partly responsible for the differences from the controls. Bryant (1973) also found a higher conduction velocity for the action potential of muscle fibres in myotonic goats as compared with normal goats.

The changes in the surface EMG and force can be interpreted as follows. Initially, the muscle fibres behave normally, but after the occurrence of several action potentials the membrane properties start to change. This results in a fast decline of the average MFCV indicating that all fibres undergo the same change. Consequently, the power spectrum shifts to the lower frequencies as can be seen from the decline in Fmed. During the first contractions, the majority of the muscle fibres subsequently undergo a depolarization block. This can be deduced from the near total disappearance of the EMG signal. As a result, the force declines. This fast reduction in MFCV during transient paresis has not been described previously. The possibility that our surface EMG recordings are to a large extent determined by myotonic runs is not likely, since Ricker *et al.* (1973) showed that these myotonic discharges disappeared during transient paresis. The amount of weakness (61–83%, *see* Table) is such that it could easily account for the movement problems of the patients.

Physiological investigations in myotonia congenita have been focused in particular on the explanation of the myotonia, and an explanation for transient paresis until now is lacking. All membrane channels studied of the naturally occurring myotonia of the goat were found to be abnormal (Bryant, 1982). Adrian and Bryant (1974) showed that in myotonic fibres action potentials resulted in an after-depolarization; the magnitude of this after-depolarization increased with increasing number of action potentials. Initially, such a depolarization could result in spontaneous discharges, subsequently leading to a depolarization block. Possibly, accumulation of potassium in the transverse tubular system is responsible for a depolarization of the surface membrane. In paramyotonia congenita the sodium channels showed an inability to close after a physiological opening (Lehmann-Horn *et al.*, 1987). In myotonic goats a slow sodium channel inactivation process was found (Bryant, 1982); this could explain the initial normal conduction followed by inexcitability due to depolarization after several action potentials. Recently, Rüdel *et al.* (1988) found an abnormal N-shaped relationship in the current-voltage relationship of the muscle membrane in a patient with myotonia congenita, which could lead to a longstanding depolarization block after the occurrence of an action potential.

The improvement during successive contractions (the warming-up phenomenon) was clearly shown. During the first maximal voluntary contraction lasting 10 s, no improvement was noted, although fast changes were sometimes observed (*see* figs 6, 7). To explain these it should be realised that the surface EMG signal is the summation of the action potentials of the active fibres. It is thus possible that the muscle fibres start to fire again in a cyclic way during the course of the contraction: after being depolarized they restart, initially with a normal conduction velocity and amplitude, only to drop out again (fig. 8). These changes in muscle membrane behaviour are very similar to the description of the spontaneous cessation of myotonic discharges in the myotonic goat. These myotonic discharges were always self-limiting and accompanied by a depolarization block. The membrane potential was found to return gradually to a normal resting value within a few seconds to minutes or could suddenly jump back to normal (Bryant, 1973).

The discrepancy we have found between the larger decline in IEMG as compared with the force can also be seen in the figures of Ricker *et al.* (1973), for example, fig. 2, and Wagner and Zett (1982). The opposite finding of a relatively larger force loss in myotonia congenita (Wiles and Edwards, 1977) remains unexplained. This discrepancy between change in force and IEMG can have different reasons. First, the force of the elbow flexion is generated by different muscles, of which one or several could be activated later during the contraction and thus ensure the generation of some force. The better accordance between the change of force and IEMG in abductor digiti minimi supports this notion (*see* Table). Secondly, the depolarization of the muscle membrane results in action potentials of lower amplitude (Trontelj *et al.*, 1987), thus disturbing the normal, more or less linear, relation between force and IEMG. Thirdly, the important frequency change of the signal could also alter the relation between force and IEMG. Since the surface electrodes act as a high-pass filter depending on the electrode separation (Zipp, 1978), the change of the signal to a lower frequency content will result in the transfer of less energy. Lastly, the possibility of a disturbance in the contraction mechanism remains, and though in paramyotonia congenita a delayed twitch relaxation was found after cold-induced paresis, this was not found in myotonia congenita (Ricker *et al.*, 1977).

The changes of force in the patients with myotonica congenita can also be described in terms of fatigue, since it fulfils the definition of fatigue: the loss of the desired or expected force (Edwards, 1981). Furthermore, this loss in force is accompanied by EMG changes normally seen in fatigue, although in a grossly exaggerated form. The decrease of the MFCV to 2.0 $\mathrm{m{\cdot}s^{-1}}$ is lower than is ever seen in controls (personal observations). It is thus possible to differentiate between various forms of pathological fatigue. We have shown, for example, that the loss in force in myasthenia gravis is accompanied by a decline in IEMG but not in MFCV, which agrees with an impairment in neuromuscular transmission as the cause of fatigue (Zwarts *et al.*, 1987*b*). The use of surface EMG in studying abnormal fatigue has also been demonstrated in McArdle's disease: the frequency spectrum shifted faster to lower frequencies during fatiguing isometric contraction than normal (Mills and Edwards, 1984) and during the adaptation phase, the IEMG was found to increase abnormally (Braakhekke *et al.*, 1986).

In conclusion, transient paresis in myotonia congenita can be described as pathological fatigue caused by membrane changes resulting in a dramatic fall in MFCV and subsequent depolarization block. In patients with myotonic dystrophy this phenomenon was not present. Our findings support the notion that the disability of the myotonia congenita patients results predominantly from transient paresis and not from stiffening of the limbs due to myotonic activity.

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RECIPROCAL INHIBITION BETWEEN FOREARM MUSCLES IN PATIENTS WITH WRITER'S CRAMP AND OTHER OCCUPATIONAL CRAMPS, SYMPTOMATIC HEMIDYSTONIA AND HEMIPARESIS DUE TO STROKE

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SUMMARY

Reciprocal inhibition of H reflexes in the forearm flexor muscles was examined in a group of 16 patients with writer's and other occupational cramps. The early disynaptic phase of reciprocal inhibition was normal. However, there was a reduction in the amount of later, presynaptic inhibition, when compared with age-matched normal subjects. Similar findings were seen in 2 patients with symptomatic hemidystonia in whom structural brain lesions were present. However, this reduction in presynaptic inhibition was not specific to patients with dystonia. In a further group of 13 patients with hemiparesis or hemiplegia due to stroke, abnormalities of both early and later phases of reciprocal inhibition were found. The patients with spasticity exhibited less disynaptic inhibition than those with normal tone or flaccid limbs. The changes in the presynaptic phase of reciprocal inhibition did not correlate with the clinical signs of spasticity and increased muscle tone. These results provide objective evidence of a physiological basis for the action or task-specific focal dystonias such as writer's cramp.

INTRODUCTION

Torsion dystonia may be classified as generalized, segmental or focal, according to the regions of the body involved (Fahn *et al.*, 1987). Each type is characterized by sustained or transient muscle contractions and spasms which twist the affected parts of the body into characteristic dystonic postures. In some patients with the clinical syndrome of torsion dystonia, a cause can be identified (symptomatic or secondary dystonia). However, in many cases investigation is unrewarding and

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such patients are described as having idiopathic or primary dystonia. Studies of patients with symptomatic forms of hemidystonia have shown structural involvement of the contralateral basal ganglia (Burton *et al.*, 1984; Marsden *et al.*, 1985; Pettigrew and Jankovic, 1985). In idiopathic torsion dystonia, however, no consistent visible structural change has been discovered in the brain on macroscopic or microscopic examination, although abnormalities of monoamines in some brain regions have been described in a few cases (Hornykiewicz *et al.*, 1986).

The pathophysiology of idiopathic dystonia remains uncertain. Physiological investigations have revealed several deficits, in addition to the abnormal level of cocontraction between agonist and antagonist muscles first described in electromyographic recordings by Hoefer and Putnam (1940). These are an increased shortening reaction (or Westphal phenomenon) (Yanagisawa and Goto, 1971), a prolongation of the long-latency stretch reflex with little effect on its latency or size (Rothwell *et al.*, 1983; Tatton *et al.*, 1984), and a reduction in the late phases of reciprocal inhibition between extensor and flexor muscles of the forearm (Rothwell *et al.*, 1983). Most of these studies were performed in patients with generalized or segmental forms of dystonia. In patients with blepharospasm, a focal cranial dystonia, a physiological abnormality also has been described (Berardelli *et al.*, 1985). The excitability cycle of the R2 component of the blink reflex is abnormal, probably due to hyperexcitability of the brainstem interneurons which mediate this response.

Writer's cramp has been proposed to be an action-specific form of focal dystonia. Two main lines of evidence support this view. First, there are patients who present only with writing difficulties, and then progress to develop dystonia in other parts of the body. Secondly, the classical features of writer's cramp, with excessive muscle cocontraction causing distortion in the posture of the fingers, hyperpronation at the wrist and elevation of the elbow, also are seen in other patients with segmental or generalized dystonia when they attempt to write. Unlike other forms of dystonia, however, no physiological or pathological abnormality has been reported in patients with writer's cramp. Because of this, its classification as a focal dystonia remains controversial. Despite the absence of psychiatric illness in such patients (Sheehy and Marsden, 1982), several authors still are inclined to dismiss writer's cramp as a psychological rather than physiological problem.

The present study was designed to test whether it might be possible to detect some underlying physiological abnormality in patients with writer's cramp. Since excessive cocontraction of the antagonist flexor and extensor muscles in the forearm is a common feature of this condition (Rothwell *et al.*, 1983; Hughes and McLennan, 1985), we tested reciprocal inhibition between these muscles in patients in comparison with normal subjects. Some of the results have been published previously in preliminary form (Rothwell *et al.*, 1983; Day *et al.*, 1987; Rothwell and Obeso, 1987).

SUBJECTS

Details of the 16 patients (aged 16–71 yrs; mean 43.6) with idiopathic writer's or other occupational cramps examined in this study are summarized in Table 1. Ten normal subjects (aged 30–64 yrs; mean 43.8) also were studied.

The diagnosis of writer's cramp was made in 13 patients on the basis of the patients' presenting complaints of difficulty with handwriting, and the typical findings on examination of widespead arm muscle spasms and dystonic posturing when writing. The group of patients with occupational cramp also included 2 with typist's cramp and 1 with musician's (pianist's) cramp. All exhibited dystonia of the affected hand when it was engaged in the relevant task. Since the findings in the latter patients did not differ from those with writing difficulty, for convenience all 16 of these patients will be described as having writer's cramp.

TABLE 1. CLINICAL FEATURES OF PATIENTS WITH IDIOPATHIC WRITER'S CRAMP OR OTHER OCCUPATIONAL CRAMPS, AND SYMPTOMATIC HEMIDYSTONIA

Case	*Age (yrs)*	*Sex*	*Duration of illness (yrs)*	*Diagnosis*
1	24	M	9	Bilateral dystonic writer's cramp
2	28	M	14	Bilateral dystonic writer's cramp
3	55	M	20	Bilateral dystonic writer's cramp
4	16	F	9	Bilateral dystonic writer's cramp
5	47	M	7	R dystonic writer's cramp
6	63	M	9	R dystonic writer's cramp
7	46	F	3	R dystonic writer's cramp
8	18	F	2	R dystonic writer's cramp
9	57	F	9	R dystonic typist's cramp
10	66	F	4	R dystonic typist's cramp
11	26	F	6	R simple writer's cramp
12	51	M	2	R simple writer's cramp
13	71	M	3	L simple writer's cramp
14	44	M	6	R simple writer's cramp
15	24	M	13	R simple writer's cramp
16	62	M	6	R simple pianist's cramp
17	20	M	19	R hemidystonia
18	76	F	17	L hemidystonia

There were no other neurological deficits on clinical examination. In particular, muscle tone and power were normal and there was no sensory loss. They had no known brain lesion. The patients with writer's cramp were divided into two subgroups on clinical grounds; simple (6 patients) and dystonic (10 patients) writer's cramp, based on the criteria of Sheehy and Marsden (1982). The patients with simple writer's cramp showed difficulty only in writing and performed other manual tasks with their affected limbs normally (i.e., a task-specific focal action dystonia). The term dystonic writer's cramp was used to refer to patients with a focal action dystonia on writing, which was also evident with many other manual acts. One of the patients with unilateral dystonic writer's cramp was taking benzhexol, but the other 15 were on no drug therapy.

Two patients with symptomatic hemidystonia also were studied. Neither was on drug treatment. They had lesions of the contralateral basal ganglia visualized on computed tomography or magnetic resonance imaging of the brain; in 1 (Case 18) an arteriovenous malformation affected the contralateral basal ganglia (fig. 1A), and in the other (Case 17) a lesion, possibly due to an internal cerebral vein thrombosis, affected the contralateral basal ganglia and adjacent white matter (fig. 1B). The clinical and radiological details of Case 17 have been reported previously (Quinn *et al.*, 1985). He had a mild action dystonia of the right face and leg, and marked spontaneous and action dystonia of the right arm. There was no detectable muscle weakness or sensory deficit, and the tendon reflexes and plantar responses were normal. Case 18 had a left hemidystonia. The left arm was held in front of her chest with adduction of the shoulder and flexion of the elbow and wrist. There was slight weakness of elbow extension and finger adduction in the upper limb and of hip and foot dorsiflexion in the left leg. The tendon reflexes were symmetric, but the left plantar response was extensor. Sensory examination was normal. This patient also developed increasing dystonic posturing of the arm and hand on attempts to perform fine manual tasks with that limb (i.e., an action dystonia).

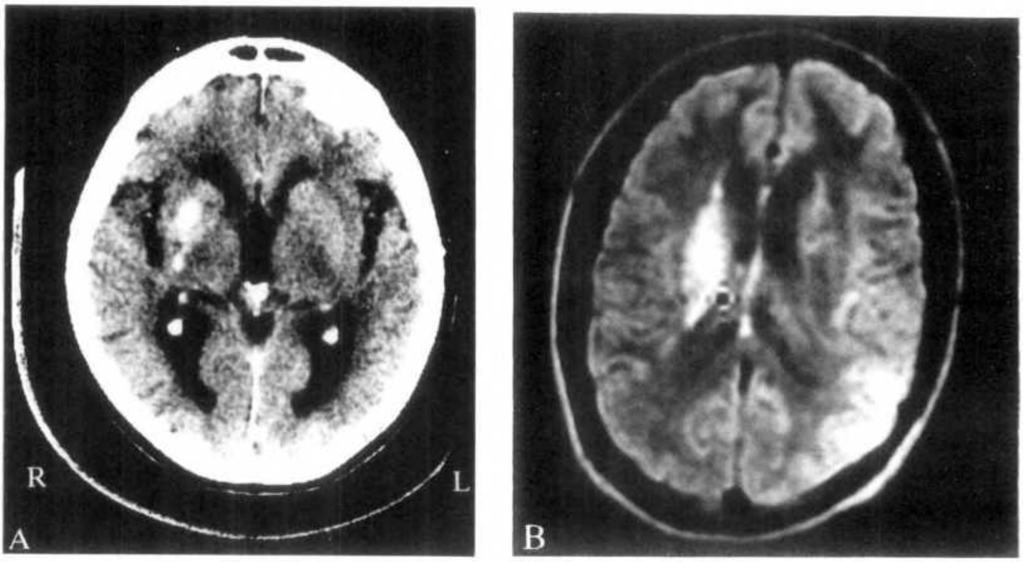

FIG. 1A, computed tomography of brain after intravenous contrast injection in *Case 18*, showing an arteriovenous malformation affecting the right basal ganglia. B, magnetic resonance imaging spin echo image (SE 1500/80) of the brain in *Case 17* showing a lesion with increased signal intensity affecting the left basal ganglia (from Quinn *et al.*, 1985, with permission).

Finally, 13 patients with hemiparesis/hemiplegia due to cerebral infarction were examined to explore the specificity of abnormalities of reciprocal inhibition (Table 2). These patients were subdivided according to their clinical features so as to examine whether variations in muscle tone correlated with changes in reciprocal inhibition. Six of the patients with hemiparesis due to stroke showed a spastic increase of muscle tone in the affected extremities; in 2, muscle tone was considered to be normal, while in 5, tone was reduced (flaccid paresis).

METHODS

In all experiments, the electromyogram (EMG) was recorded from surface electrodes placed over the bellies of the relaxed forearm wrist and finger flexor muscles of the affected arm. Subjects were seated, with the forearm pronated and resting on the arm of the chair. The EMG was amplified by

TABLE 2. CLINICAL FEATURES OF PATIENTS WITH STROKE

Case	*Age (yrs)*	*Sex*	*Interval after stroke (months)*	*Site of lesion*	*Symptom*	*Muscle tone*
19	29	M	1	R internal capsule	L Hemiplegia	+
20	43	M	16	R fronto-parieto-temporal	L hemiparesis L hemianaesthesia	+
21	68	M	2	R fronto-parieto-temporal	L hemiparesis L hemianaesthesia	+
22	67	F	18	R fronto-parieto-temporal	L hemiparesis	+
23	72	F	2	L internal capsule	R hemiparesis	+
24	53	M	3	R fronto-parietal	L hemiparesis L hemianaesthesia	+
25	52	M	2	R internal capsule*	L hemiparesis	0
26	60	M	2	L internal capsule	R hemiparesis	0
27	63	M	2	pons	R hemiplegia	—
28	59	M	1	L fronto-parietal	R hemiplegia	—
29	48	M	3	L internal capsule	R hemiplegia	—
30	79	M	1	L fronto-parietal	R hemiparesis	—
31	60	F	2	L internal capsule*	R hemiparesis	—

Muscle tone: + = increased (spastic); 0 = normal; — = reduced. * Location of lesion inferred from clinical findings. Otherwise lesion identified on CT or MRI.

Digitimer D150 amplifiers, and band-pass filtered 3 dB down at 53 Hz–3.0 kHz. Data was collected by a Digitimer D200 computer.

H reflexes in the forearm muscles were tested by electrical stimulation of the median nerve in the antecubital fossa. Low intensity stimuli of 0.5 ms duration were applied to the median nerve at 5 s intervals to elicit approximately half maximal H reflexes in wrist and finger flexor muscles. Three kinds of conditioning stimuli were used; electrical radial nerve stimulation in the spiral groove (Day *et al.*, 1984; Rothwell *et al.*, 1983; Berardelli *et al.*, 1987; Rothwell and Obeso, 1987), mechanical tap stimulation to the wrist and finger extensor muscle bellies; and electrical stimulation of the superficial (cutaneous) branch of the radial nerve at wrist (Berardelli *et al.*, 1987).

Reciprocal inhibition produced by radial nerve stimulation

Reciprocal inhibition of the forearm flexor motoneurons from the antagonist extensor muscle afferents was produced by single, low intensity, electrical shocks to the radial nerve in the spiral groove. The stimulus intensity was set to be at or just above the threshold of the wrist extensor muscle M response, which was simultaneously monitored by surface EMG. The median nerve was stimulated at various time intervals between −2 and 100 ms before and after the conditioning radial nerve shock. At each time interval, the occurrence of the conditioning shock was randomized between trials; 12–20 sets of unconditioned and conditioned H reflexes were averaged and their peak-to-peak size measured. The size of the conditioned H reflex was expressed as a percentage of the size of the unconditioned H reflex at each time interval.

The time required to complete each investigation meant that it was not always possible to study precisely the same range of conditioning-test intervals in all subjects. As a result, in the figures illustrating the time course of inhibition, some points have been plotted which do not contain data from all subjects. The minimum number of contributing individuals is given in each figure. However, the important periods, at intervals between the radial and median nerve shocks of 0, ±0.5, and ±1 ms, which reflect disynaptic inhibition of flexor motoneurons (Day *et al.*, 1984), and at 10 and 20 ms, which reflect presynaptic inhibition of flexor Ia afferent terminals (Berardelli *et al.*, 1987), were studied in every subject. The maximal amount of early disynaptic inhibition was usually seen at a time interval of 0 ms although this varied by ±0.5 ms in some subjects. In each subject the time interval when the maximal amount of early disynaptic inhibition was seen is referred to as the time interval of 0 ms.

Inhibition of H reflex produced by mechanical tap to extensor muscles

Pierrot-Deseilligny and colleagues (Morin *et al.*, 1984; Hultborn *et al.*, 1987) have described a slightly different method of studying presynaptic inhibition of Ia afferent terminals, which we compared with our electrical method. In the leg, it has been shown that weak and short-lasting vibration (3 cycles at 200 Hz) applied to the skin over the tibialis anterior muscle causes pure presynaptic inhibition of a soleus test H reflex given 25–60 ms later. In order to adapt this to the arm, we used an electromagnetic vibrator (Ling Dynamic Systems Ltd) to give a single 5 ms duration tap of less than 0.5 mm amplitude to the skin overlying the extensor compartment of the forearm. Inhibition of the flexor H reflex was tested over time intervals of 30–100 ms later. Nine patients were studied with this technique (5 with simple and 4 with dystonic writer's cramp).

Cutaneous facilitation of H reflex

Single stimuli delivered to the superficial radial nerve produced facilitation of flexor forearm H reflexes at time intervals of 30–50 ms (Berardelli *et al.*, 1987). The extent of this effect was compared in normal subjects and in patients with writer's cramp. Stimuli of 0.5 ms duration were given to the superficial radial nerve at an intensity of twice sensory threshold, and at intervals ranging from 20–60 ms before the median nerve stimulus. The conditioning-test interval was adjusted by 7 ms to compensate for the conduction time between the wrist and the usual stimulation site of the radial nerve in the spiral groove (Berardelli *et al.*, 1987). The peak-to-peak size of the conditioned H reflex was expressed as a percentage of the unconditioned H reflex as described above. Ten patients were studied with this technique (4 with simple and 6 with dystonic writer's cramp).

Statistical comparisons were made using analysis of variance (ANOVA) with repeated measures. In the study of reciprocal inhibition produced by radial nerve stimulation, analysis of variance was used for data reflecting disynaptic reciprocal inhibition at the time intervals of −0.5, 0, 0.5 and 1 ms, and for data reflecting presynaptic inhibition at time intervals of 10 and 20 ms after the radial nerve shock.

RESULTS

Writer's cramp

Reciprocal inhibition produced by radial nerve stimulation. In normal subjects, the time course of inhibition of the flexor H reflex produced by conditioning radial nerve shocks showed three distinct phases (fig. 2). The timing of the first phase (fig. 2A), which was maximal at a conditioning test interval of 0 ms, was compatible with Ia disynaptic inhibition of flexor motoneurons by activation of large diameter afferents from extensor muscles (Day *et al.*, 1984). This was followed by two much longer lasting phases from 5 to 30 ms and from 50 to at least 100 ms (fig. 2B). It is thought that at least the earlier of these latter phases reflects presynaptic inhibition of the terminals of flexor Ia afferent fibres (Berardelli *et al.*, 1987). Since we have no definitive information on the possible mechanism responsible for the third phase of H reflex inhibition, the remainder of the analysis in this paper will be confined to the first and second phases.

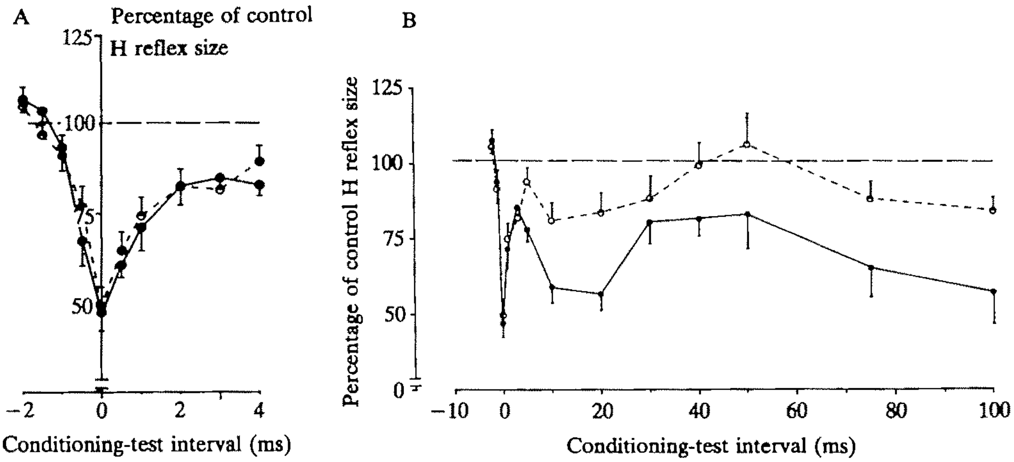

FIG. 2. Inhibition of the forearm flexor H reflex when tested at different times after a single motor threshold conditioning stimulus (at t = 0 ms) given to the radial nerve in the spiral groove. Negative timings indicate that the median nerve test shock (used to elicit flexor H reflexes) was given before the conditioning (radial nerve) shock. A, time course of the first (disynaptic) phase of flexor H reflex inhibition produced by radial nerve stimulation. B, time course of the first, second and third phases of flexor H reflex inhibition produced by radial nerve stimulation. Mean (±1 SE) values of the size of the flexor H reflex, expressed as a percentage of control H reflexes, are plotted. Normal subjects (●—●) (n = 10); patients with writer's cramp (○---○) (n = 16). All subjects and patients contributed data to timings at −1, −0.5, 0, +0.5, +1, +10, and +20 ms. Data points at other timings are averages from at least 7 normal subjects and 12 patients (*see* Methods).

The time course and depth of the early short-duration disynaptic inhibition was normal in the affected arms of the 16 patients with writer's cramp (ANOVA: $f(1,24) = 0.86$, $P > 0.05$) (fig. 2A). In contrast, there was a reduction in the amount of the second phase of reciprocal inhibition in these patients (ANOVA: $f(1,24) = 9.26$, $P < 0.005$) (fig. 2B). These results also are presented in Table 3.

The patients were divided on clinical criteria (*see* Methods) into two subgroups of simple (6 patients) and dystonic (10 patients) writer's cramp. The first, disynaptic, phase of reciprocal inhibition was normal in both groups of patients (fig. 3), whereas the second, presynaptic, phase at 10 and 20 ms was abnormal (ANOVA: simple writer's cramp $f(1,14) = 4.66$, $P < 0.05$; dystonic writer's cramp

TABLE 3. AVERAGE VALUES FOR DISYNAPTIC (INTERVAL 0) AND PRESYNAPTIC (INTERVAL, 10, 20 ms) INHIBITION OF WRIST AND FINGER FLEXOR MOTONEURONS IN THE PATIENTS STUDIED

	Interval (ms)		
Case	*0*	*10*	*20*
1	44	54	82
2	33	99	105
3	41	100	127
4	20	39	52
5	70	108	94
6	49	121	119
7	61	90	90
8	24	81	71
9	26	71	114
10	77	54	48
11	64	94	88
12	18	93	66
13	68	56	56
14	53	78	76
15	87	84	96
16	46	64	43
17	39	74	83
18	71	86	96
19	99	102	103
20	92	81	85
21	92	108	86
22	85	85	86
23	81	55	84
24	65	72	83
25	74	76	93
26	69	102	95
27	81	73	68
28	64	61	58
29	63	93	115
30	49	70	67
31	34	55	51
Normal values	47±32	58±32	56±32 (mean±2 SD)

Values given are expressed as a percentage control.

f (1,18) = 9.68, $P < 0.001$). There was a tendency for this second phase to be more abnormal in those patients with dystonic writer's cramp than in those with simple writer's cramp, but this was not statistically significant (ANOVA: f (1,14) = 1.0, $P > 0.05$).

The results in the 2 patients with dystonic typist's cramp were very similar to those in patients with dystonic writer's cramp. Thus the depth of initial disynaptic inhibition was to 24 and 33% of baseline values, compared with a mean of 47%

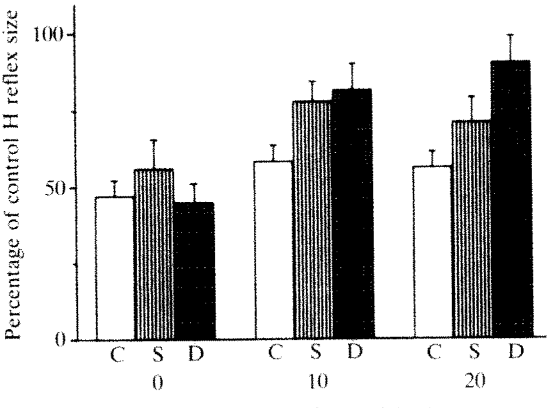

FIG. 3. Inhibition of the forearm flexor H reflex produced by electrical radial nerve stimulation in patients with simple and dystonic writer's cramp. The three groups of bars show data at conditioning test intervals of 0 ms (disynaptic inhibition) and 10 and 20 ms (presynaptic inhibition). C = 10 normal subjects; S = 6 patients with simple writer's cramp; D = 10 patients with dystonic writer's cramp. Mean (± 1 SE) values of the size of the test flexor H reflex, expressed as a percentage of control H reflex are shown.

in the control subjects. The depth of second phase inhibition at 10 ms was only to 81 and 99%, and at 20 ms was to 71 and 105%, respectively, compared with control values of 58% at 10 ms and 56% at 20 ms. The results in the patient with simple pianist's cramp were similar to those in patients with simple writer's cramp. Thus disynaptic inhibition was to 18%, while inhibition at 10 ms was to 92% and at 20 ms was to 54%.

Reciprocal inhibition produced by tapping the forearm extensor muscle. In 7 normal subjects, forearm flexor H reflexes were suppressed by a tap to the forearm extensor muscles for conditioning-test intervals of from 40 ms up to 100 ms (fig. 4). However, in 9 of the patients with writer's cramp the tap induced little or no inhibition of flexor H reflexes (ANOVA: f (1,14) = 7.69, $P < 0.025$).

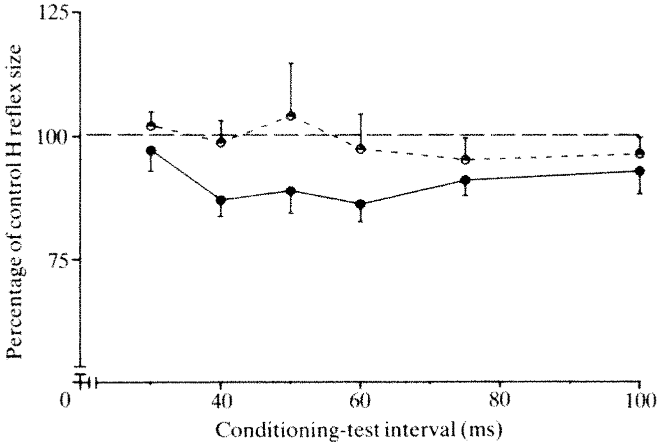

FIG. 4. Inhibition of the forearm flexor H reflex produced by a tap applied to the forearm extensor muscles. Time courses of flexor H reflex inhibition in 7 normal subjects (●——●) and 9 patients with writer's cramp (5 patients with simple writer's cramp and 4 with dystonic writer's cramp) (○- - -○) are shown. Mean (± 1 SE) values of the size of the test flexor H reflex, expressed as a percentage of control H reflex, are plotted for time intervals between 30 and 100 ms.

Cutaneous facilitation. It is possible that the reduction in the amount of inhibition of the flexor H reflex by radial nerve shocks at conditioning-test intervals of 10 and 20 ms in patients with writer's cramp might not have been caused by a deficit in presynaptic mechanisms, but by the superimposition of an extra facilitation from some other source. Possible candidates for such facilitation are large diameter cutaneous afferents in the radial nerve, which may have been activated by the motor threshold conditioning radial nerve stimulus (*see* Berardelli *et al.*, 1987). To test this possibility, the facilitation of flexor H reflexes following stimulation of the superficial (cutaneous) branch of the radial nerve was studied.

In normal subjects, H reflexes were increased in size for intervals of 30–60 ms after cutaneous stimulation (fig. 5). There was no difference in the amount or time course of this facilitation between 10 of the patients with writer's cramp and the 10 normal subjects (ANOVA: f (1,18) = 0, $P > 0.05$).

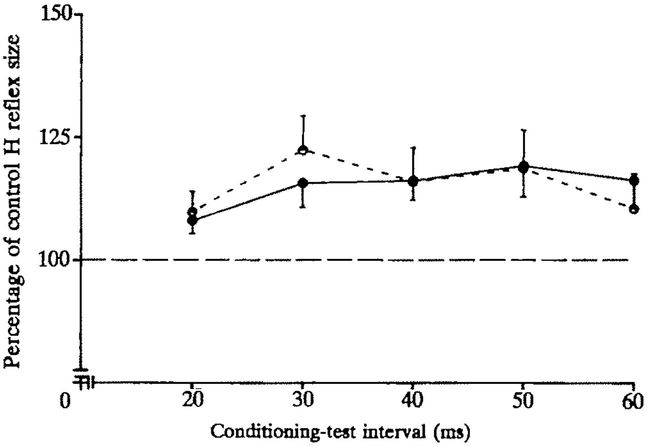

FIG. 5. Cutaneous facilitation of the forearm flexor H reflex produced by stimulation of superficial cutaneous branch of the radial nerve. Time course of flexor H reflex facilitation after superficial radial nerve stimulation in 10 normal subjects (●——●) and 10 patients with writer's cramp (4 with simple writer's cramp and 6 with dystonic writer's cramp) (o----o) is shown. Mean (±1 SE) values of the size of the test H reflex, expressed as a percentage of control H reflex, are plotted for time intervals between 20 and 60 ms.

Reciprocal inhibition in symptomatic hemidystonia

The results from the affected side in the 2 patients with symptomatic hemidystonia are plotted in fig. 6 together with the mean normal data. Initial disynaptic inhibition (conditioning-test interval of 0 ms) to 39% and 71% was well within the normal range. However, both patients exhibited a reduction in the second phase of inhibition of flexor H reflexes by radial nerve shocks. At a conditioning-test interval of 20 ms, the inhibition in Case 18 to 96% of baseline, and that in Case 17 to 83% was less than normal (mean inhibition to 56%). Mean inhibition in the normal arm of Case 17 at 20 ms was to 62%.

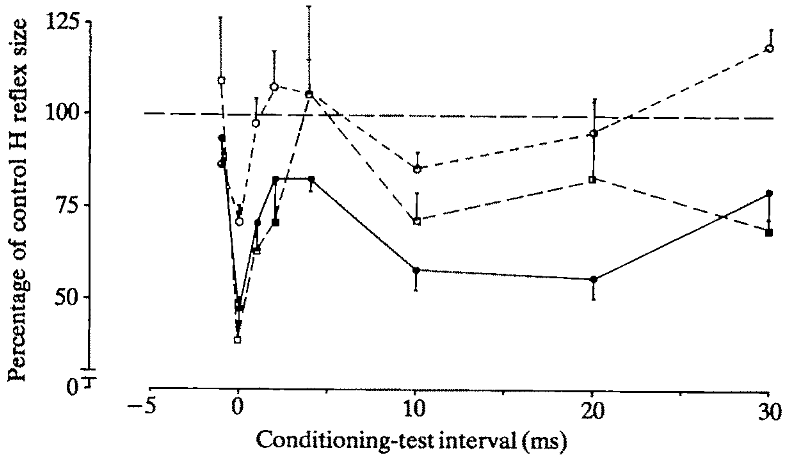

FIG. 6. Time course of reciprocal inhibition of the forearm flexor H reflex produced by electrical radial nerve stimulation in patients with symptomatic hemidystonia. Two patients with symptomatic hemidystonia were studied. Both patients showed reduction of the later presynaptic phase of reciprocal inhibition. Control (●——●), *Case 17* (□——□), *Case 18* (○——○). Control values are those shown in fig. 1B. In the patients, each point represents the mean (±1 SE) of 10 observations of the sizes of the flexor H reflex, expressed as a percentage of control H reflex.

Reciprocal inhibition in patients with hemiparesis caused by stroke

In this group of patients, four patterns of reciprocal inhibition were observed (fig. 7): normal (fig. 7A), normal disynaptic phase with abnormal presynaptic phase (fig. 7B), abnormal disynaptic phase with normal presynaptic phase (fig. 7C), and abnormal disynaptic and presynaptic phases (fig. 7D). When the data from all 13 patients in this group were combined, there was a clear reduction in the depth of both first and second phases of reciprocal inhibition (fig. 8). These results are shown in Table 3.

Since Delwaide (1985) has suggested that there may be a correlation between the degree of spasticity and a disorder of reciprocal inhibition, we divided these patients into two groups according to their muscle tone. There were 6 patients with spasticity and 7 patients without spasticity. Both subgroups of patients showed significantly less inhibition in both the first and second phases than normal subjects (ANOVA: spastic group, first phase (including data from intervals −1, −0.5, +0.5, +1.0 ms, not plotted in fig. 8): f (1,14) = 44.71, $P < 0.005$, second phase: f (1,14) = 14.67, $P < 0.005$); normal or flaccid group, first phase f (1,15) = 15.06, $P < 0.05$, second phase f (1,15) = 5.66, $P < 0.05$) (fig. 8). However, the amount of reciprocal inhibition in the disynaptic phase was significantly less in patients with spasticity than it was in the patients with normal tone or a flaccid paresis (ANOVA: f (1,11) = 5.4, $P < 0.05$). The presynaptic phases did not differ between the two subgroups (ANOVA: f (1,11) = 0.93, $P > 0.05$).

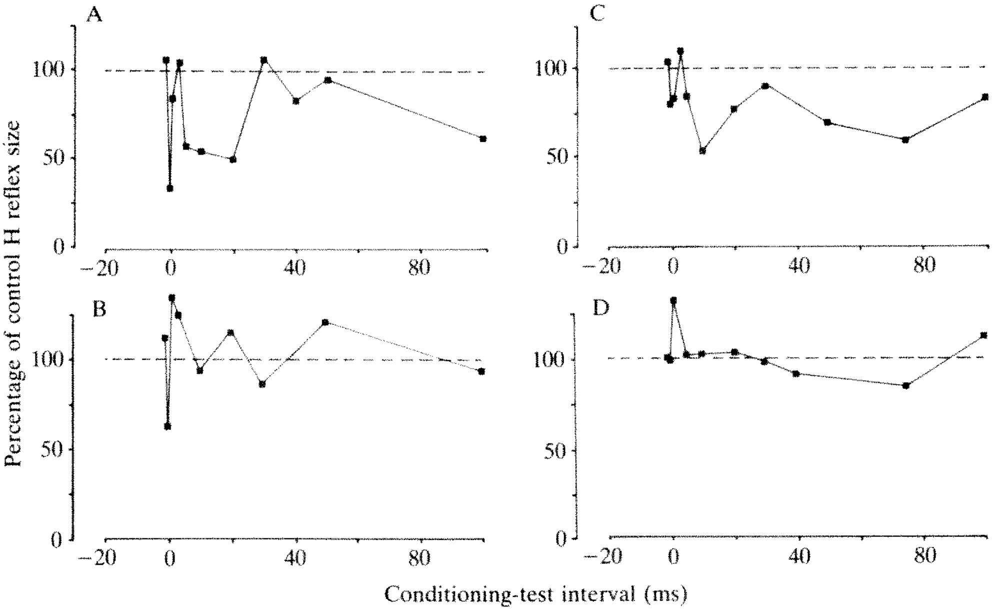

FIG. 7. Reciprocal inhibition of the forearm flexor H reflex produced by electrical radial nerve stimulation in 4 representative patients with hemiparesis caused by stroke. Patients with hemiparesis caused by stroke showed four patterns of reciprocal inhibition. A, normal pattern (*Case 31*); B, normal disynaptic phase and abnormal presynaptic phase (*Case 29*); C, abnormal disynaptic phase and normal presynaptic phase (*Case 23*); D, abnormal disynaptic and presynaptic phases (*Case 19*). Each point represents the mean of 10 observations. The sizes of the test H reflex are expressed as a percentage of control H reflex.

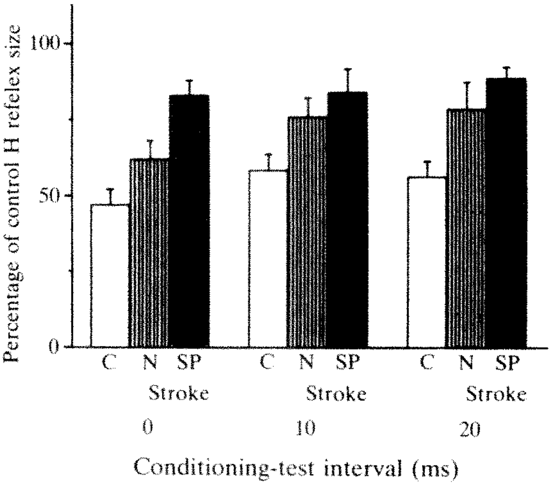

FIG. 8. Reciprocal inhibition produced by electrical radial nerve stimulation in stroke patients with and without increased muscle tone. Patients with normal or reduced muscle tone (N) and with spasticity (SP) are compared with normal control subjects (C) for the disynaptic phase of reciprocal inhibition at a conditioning-test interval of 0 ms, and for the presynaptic phase of reciprocal inhibition at 10 and 20 ms. Mean (±1 SE) values of the sizes of the test flexor H reflex, expressed as a percentage of control H reflex, are shown.

DISCUSSION

This study has examined reciprocal inhibition from extensor to flexor muscles of the forearm in patients with simple or dystonic writer's cramp, symptomatic hemidystonia and upper motor neuron syndromes due to cerebral infarction. Reciprocal inhibition was examined using both electrical stimulation of the radial nerve in the spiral groove, and with weak taps to the belly of the extensor muscles. Using the electrical method, we found that the first disynaptic phase (Day *et al.*, 1984) of inhibition was normal in patients with writer's cramp, but that the depth of the second, presynaptic phase (Berardelli *et al.*, 1987) of inhibition was reduced. Morin *et al.* (1984) have provided strong evidence that small muscle taps also produce a predominantly presynaptic inhibition of large muscle afferents at conditioning-test intervals of about 40 ms. This inhibition also was reduced in patients with writer's cramp.

One possible explanation for these changes is that presynaptic inhibition in the patients is obscured by some concurrent facilitation from some other source. A likely candidate would be enhanced cutaneous facilitation from large diameter cutaneous afferents in the radial nerve which are known to excite flexor H reflexes at conditioning-test intervals of 30–40 ms. In the present study, however, stimulation of the superficial cutaneous branch of the radial nerve produced normal cutaneous facilitation in these patients, so this is unlikely to explain the present results. We presume that there is indeed a reduction in the amount of presynaptic inhibition from large diameter afferents in the radial nerve onto the terminals of Ia afferents from flexor muscles in patients with writer's cramp.

Patients with simple writer's cramp had an abnormality of the presynaptic phase of reciprocal inhibition similar (but perhaps less marked) to that seen in dystonic writer's cramp. In addition, abnormalities of the second phase of inhibition were seen in the 2 patients with dystonic typist's cramp, and the 1 patient with simple pianist's cramp. This may indicate that the same underlying deficit was present in all these patients. However, larger numbers are required to establish this point unequivocally.

There are three possible mechanisms which might account for the reduction in presynaptic reciprocal inhibition. (1) A disorder of presynaptic contacts onto the group I afferent terminals. (2) Pathological changes in the interneurons mediating presynaptic inhibition. (3) Defective descending control of the excitability of the presynaptic inhibitory pathway.

Of these options we favour the third, since what is known of the pathology of dystonia suggests a defect in the basal ganglia and its connections rather than in the spinal cord. In addition, similar changes in presynaptic inhibition were observed in patients with demonstrable structural lesions in the brain. These included 2 patients with symptomatic hemidystonia due to lesions of the contralateral basal ganglia, and others with hemiparesis and hemiplegia due to cerebral infarction. Our hypothesis, therefore, is that in writer's cramp the postulated basal ganglia dysfunction produces a disorder of descending control of those spinal interneurons which mediate group I presynaptic inhibition of Ia afferent terminals. These results are similar to data presented recently by Panizza *et al.* (1987). They also found that the second phase of reciprocal inhibition was decreased in patients with writer's cramp but, in addition, there was also a reduction in the amount of early disynaptic inhibition although the reason for this discrepancy is not clear. There may have been differences in methodology (M. Hallett, personal communication): their patients were lying, ours were seated; their conditioning radial nerve stimulation was below motor threshold, ours was just suprathreshold. The implication is that under certain conditions, abnormalities of spinal interneuronal pathways other than the presynaptic inhibitory route, may become evident.

Two features of the present results are of interest. First, the deficit was present in patients who were at rest, and secondly, the disynaptic reciprocal inhibitory mechanism in the same patients appeared to be normal. This means that the abnormal descending input which controls the excitability of presynaptic spinal interneurons must (1) be present at rest, and (2) be capable of projecting separately to the interneurons mediating presynaptic as against disynaptic inhibition.

There is evidence from animal work to support this model. In the lumbar spinal cord of the cat, presynaptic inhibition of Ia afferents by group I afferents from antagonist muscles is mediated by a trisynaptic linkage (Jankowska *et al.*, 1981; Rudomín *et al.*, 1983). The group of interneurons in this pathway receive both excitatory and inhibitory projections from a variety of supraspinal centres via pyramidal, rubrospinal, vestibulospinal and reticulospinal tracts (Carpenter *et al.*, 1963; Hongo and Jankowska, 1967; Cook *et al.*, 1969; Hongo *et al.*, 1972; Baldissera *et al.*, 1981; Rudomín *et al.*, 1983). These interneurons concerned with presynaptic inhibition are separate from the Ia inhibitory interneurons which mediate disynaptic reciprocal inhibition and which also receive diverse supraspinal projections (*see* Baldissera *et al.*, 1981).

It is not clear whether the descending inputs to these two sets of interneurons are separate in the cat. However, in man there is evidence to support the notion of a very careful control of specific groups of spinal interneurons from higher centres. For example, presynaptic inhibition of Ia afferent terminals onto the motoneurons of contracting human leg muscles is decreased at the onset of (Hultborn *et al.*, 1987) or during (Iles and Roberts, 1986, 1987) a voluntary contraction, while presynaptic inhibition of Ia terminals onto motoneurons of other muscles may be increased (Hultborn *et al.*, 1987). Ia inhibitory interneurons have been shown to receive a corticospinal input in man (Rothwell *et al.*, 1984), and also are subject to descending control at the onset and during voluntary muscle contraction (Tanaka, 1974; Day *et al.*, 1983, 1984). In view of these data it seems likely that abnormalities in reciprocal inhibition seen in the patients with writer's cramp do indeed result from defects in the descending control of spinal interneurons. Our postulate is that basal ganglia damage can influence a specific group(s) of pathways which have a tonic influence on presynaptic inhibitory interneurons in the spinal cord.

This type of explanation can be applied to the results seen in patients with hemiplegia. In contrast to patients with writer's cramp or symptomatic hemidystonia, patients with hemiplegia caused by stroke exhibited various combinations of deficits in disynaptic and presynaptic reciprocal inhibition. Presumably the central projections to both groups of interneurons could be affected by a stroke. It is possible, for example, that the corticospinal pathway may have a preferential tonic input to the Ia inhibitory interneurons, whereas a reticulospinal route may have a preferential tonic input to presynaptic inhibitory interneurons. Both pathways might be affected by cerebral infarction, whereas the basal ganglia may influence the reticulospinal route more strongly, perhaps via direct connections from medial globus pallidus and substantia nigra pars reticulata.

Finally, can the deficit in reciprocal inhibition that we have described in writer's cramp explain the abnormality of movement control exhibited by these patients? There are no conclusive data on this point. The experiments were performed at rest, while the cramp is an action-induced dystonia. Further abnormalities in the descending control of spinal circuits may become apparent during voluntary movement. However, it is encouraging to have found a physiological abnormality in a disease once thought to have a purely psychiatric origin.

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OBSESSIVE-COMPULSIVE AND OTHER BEHAVIOURAL CHANGES WITH BILATERAL BASAL GANGLIA LESIONS

A NEUROPSYCHOLOGICAL, MAGNETIC RESONANCE IMAGING AND POSITRON TOMOGRAPHY STUDY

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SUMMARY

Eight patients are reported who shared the combination of bilateral basal ganglia lesions and a frontal lobe-like syndrome. The main features were inertia and loss of drive, with preservation of intellectual function. Some patients showed stereotyped activities with compulsive and obsessive behaviour which were sometimes highly elaborate in pattern. Extrapyramidal clinical signs were absent or mild. Brain damage, related to anoxic or toxic encephalopathy, was demonstrated by CT scans and MRI. The lesions appeared to be confined to the lentiform nuclei, particularly affecting the pallidum, although there was generalized brain atrophy in 2 cases. Positron emission tomography (PET) in 7 patients revealed hypometabolism of the prefrontal cortex relative to other parts of the brain. The PET studies suggest dysfunction of the prefrontal cortex as a result of damage to the lentiform nuclei. These clinical, anatomical and functional observations emphasize the role of the circuits linking the prefrontal associative cortex and some specific areas of the neostriatum, including the pallidum. The existence of distinct nonoverlapping circuits in the motor field or in the associative field can explain the fact that basal ganglia lesions may give rise to a clinical picture that is either purely motor, purely behavioural (as in some of our patients), or both. Similarities existed between some symptoms found in our patients and certain features of major psychiatric illnesses such as severe depression, catatonic schizophrenia, and obsessive-compulsive disorder. This raises the hypothesis that some aspects of these psychiatric disorders could be related to structural and physiological disturbances in the systems linking the frontal associative cortex and the basal ganglia.

INTRODUCTION

The symptoms reported in cases of damage to the lentiform nucleus generally consist of motor disturbances (Marsden, 1982). We have previously reported

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instances where patients with bilateral lesions of the lentiform nuclei without or with very mild extrapyramidal symptoms, presented unusual behavioural abnormalities (Laplane *et al.*, 1981, 1982, 1984). The symptoms, which were summarized as a 'loss of drive', included a marked decrease in spontaneous activity, a loss of affect, and a notable reduction of spontaneous thought content. Also remarkable was the observation that their inertia was apparently reversible by external stimulation, such as the incitement by a relative. Moreover, on neuropsychological testing, intellectual capacities were largely preserved, except for a memory defect in 1 of the 3 cases.

The attributability of these disturbances to lesions of the lentiform nuclei was strongly suggested by the CT scan findings, but doubt remained as to the possibility of diffuse or multifocal brain damage, in spite of the normality of EEG recordings and the absence of other visible lesions on the scan images. In addition, the question was raised as to how these limited subcortical lesions could induce such behavioural changes. The hypothesis of a functional impairment of the prefrontal cortex was made on the basis of strong clinical resemblances between our patients' symptoms and a frontal lobe syndrome. This similarity, and the absence of motor disturbance, led to the suggestion that the lesions might have affected the 'association' circuits linking some compartments of the basal ganglia and the prefrontal cortex. Finally, the additional presence, in 2 of these 3 patients, of obsessive-compulsive behaviour was noteworthy, representing a likely example, if confirmed by further cases, of psychiatric symptoms being produced by focal brain impairment.

Since then, 2 other cases have been reported by Ali-Cherif *et al.* (1984) and we have now been able to examine 5 new similar cases. It was possible to perform magnetic resonance imaging (MRI) and positron emission tomography (PET) in 7 of our 8 cases, and in the light of this additional material, some progress can be made towards the understanding of the clinical features.

MATERIAL AND METHODS

All 8 patients were selected on the basis of symptoms of inertia, reversible under stimulation and the presence of lesions of the lentiform nuclei on CT scans.

Neuropsychological testing

Intellectual function and memory. The following tests were selected: the Wechsler Verbal Scale, the Raven's 1938 Progressive Matrices (PM 38) and the Wechsler Memory Scale. Patients were allowed unlimited time to perform these tests.

Frontal lobe function. The simplified version of the Wisconsin Card Sorting test (Nelson, 1976), tests of verbal fluency (names of animals in 1 min, words beginning with the letter M in 1 min) (Benton, 1968), and a graphic series (Luria, 1966) were chosen because they were known to be sensitive to frontal lobe dysfunction. Behavioural abnormalities (prehension, imitation and utilization), observed in patients with frontal lobe lesions (Lhermitte, 1983; Lhermitte *et al.*, 1986) were also evaluated.

Linguistic, gestural and drawing tests. These included the naming of objects, writing a sentence on dictation, calculation, execution of symbolic gestures, and the copying of a cube or the Rey-Osterrieth complex figure.

The 15 objects test (B. Pillon *et al.*, unpublished). This visual discrimination task, consisting of 15 superimposed images of objects, was chosen in order to evaluate cognitive slowing.

Objective personality tests. The Minnesota Multiphasic Personality Inventory (MMPI) or a self-rating depression scale (Pichot *et al.*, 1984) was used.

Magnetic resonance imaging

In 7 patients (Cases 2–8), MRI was performed on a superconducting MR imager operating at a field strength of 1.5 T. Coronal and horizontal (Virschow's plane) 5 mm slices were taken every 7.5 mm. T1 and T2 weighted sequences were used. Real-size printed photographs were obtained from the films and were compared with atlases (Salamon and Huang, 1980, for CT, and Roberts *et al.*, 1987, for MRI) in order to delineate the lesions.

Positron emission tomography

In 7 patients (Cases 2–8) regional cerebral glucose utilization (rCMRglu) was measured using the ^{18}F-fluorodeoxyglucose (^{18}FDG) technique as applied to PET using methods as described elsewhere (Phelps *et al.*, 1979; Baron *et al.*, 1982). Six PET studies were performed on the multiring LETI. TTV01 time-of-flight tomograph. Seven planes parallel to the orbitomeatal (OM) line and located respectively at 10, 25, 40, 55, 70, 85 and 100 mm above this line were obtained simultaneously. The axial and lateral resolutions were equal to 13 mm FWHM with an undetected interslice of about 3 mm. One study (Case 4) was performed on the single slice ECATII tomograph (lateral resolution was about 16 mm and slice thickness about 19 mm) and only 3 planes were studied (OM line +18, 38 and 58 mm, respectively). All images were corrected for attenuation using 68Ge-68Ga transmission scans. The PET scans were acquired from 40–56 min after the injection of about 7 mCi of ^{18}FDG. The time course of the changes in plasma ^{18}FDG concentration was obtained by means of serial arterial blood samples collected via a radial arterial catheter. The study was performed on subjects at rest with their eyes closed but ears unplugged, without significant external stimulation. Quantitative CMRglu images, in mg/100 g/min were obtained from the raw ^{18}FDG images using the in vivo 'autoradiographic' method developed by Phelps *et al.* (1979). This was accomplished using the operational equation which contained the 4 FDG rate constants (including the dephosphorylation constant rate k4) measured in 13 young healthy volunteers, the 'lumped constant' estimated at 0.42, the pixel ^{18}FDG concentration at time of study (decay-corrected), the time course of arterial plasma ^{18}FDG concentration from injection time to acquisition time, and the plasma glucose content (mean of 5 determinations during the study).

PET data analysis. In order to compensate for the intersubject variability in head shape among patients and controls, 5 typical brain planes out of the 7 original PET cuts were selected from each study according to the atlas of the human brain of Matsui and Hirano (1978); these 5 typical planes, on which the 'region of interest' (ROI) positioning procedure was applied (*see* below), were the 'cerebellar cut', the 'frontobasal cut', the 'basal ganglia cut', the 'low centrum semiovale cut' and the 'high centrum semiovale cut' (labelled planes I, II, III, IV and V, respectively). In the present report, only the analysis for planes II–V will be given (fig. 1). The rCMRglu of the cerebral cortex was assessed by means of 3 cm^2 circular ROIs positioned over the cortical rim for each of the 4 selected planes using a standardized method detailed elsewhere (Samson *et al.*, 1986). The set of ROIs, defined first for the right cerebral hemisphere, was then automatically mirror copied over the left side with respect to the anteroposterior sagittal axis; in addition, one ROI was positioned in the medial frontal cortex of each plane. This method of ROI positioning is widely used as an objective procedure because the ROIs are positioned along the cortical rim, tangentially to one another (starting lateral to the medial frontal ROI) (fig. 1). The original ROIs were subsequently grouped within each one of the PET slices according to anatomical regions (Matsui and Hirano, 1978) as explained in the legend of fig. 1. After averaging the ROI CMRglu values of each anatomical region, this procedure yielded 13 cortical regions on each side, and 4 medial frontal regions, for a

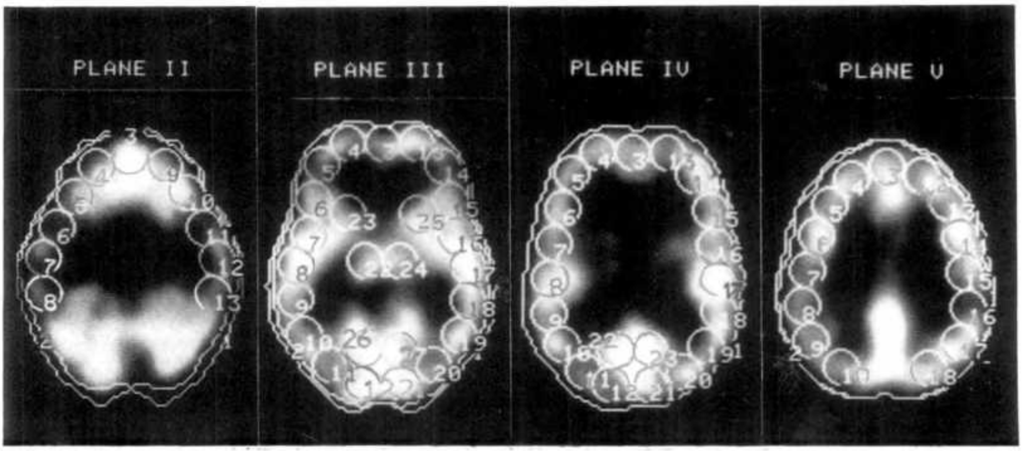

FIG. 1. Set of circular regions of interest (ROIs) used to define on the PET images the 'anatomical' regions over the cortical and subcortical structures on planes II ('frontobasal cut'), III ('basal ganglia cut'), IV ('low centrum semiovale cut') and V ('high centrum semiovale cut'). The cortical ROIs were positioned over the cerebral cortex tangentially to one another as well as to the computer-defined outer 30% isocontour (ROI 1). On plane II: the mediofrontal area (3) and on the left hand side (the right hemisphere): the laterofrontal (4, 5) and the temporal (7, 8) areas (ROI 6 was not used); on plane III: the mediofrontal (3) and on the left hand side the laterofrontal (4, 5, 6), the temporal (7, 8), the temporo-occipital (9, 10, 11), the occipital (12–26), the thalamic (22) and the striatal (23) areas; on plane IV: the mediofrontal (3), and on the left: the laterofrontal (4, 5, 6), the temporal (7, 8), the temporo-occipital (9, 10, 11) and the occipital (12–22) areas; on plane V: the mediofrontal (3), the laterofrontal (4, 5, 6), the parietal (7, 8) and the parieto-occipital (9, 10) areas. Symmetric ROIs were copied automatically on the left hemisphere with respect to an anteroposterior sagittal axis defined visually in such a way that the mirror 30% isocontour (ROI 2) was roughly superimposed over the original 30% isocontour (ROI 1).

total of 30 regions. For the ECATII data (Case 4), only 2 cuts across the cerebral hemispheres were available (OM + 38 mm and OM + 58 mm), providing a set of 12 regional CMRglu results.

The data analysis was carried out not only on the absolute rCMRglu values, but also on 'metabolic ratios' (or indices) which were calculated as rCMRglu divided by the average ipsilateral cortical CMRglu (the mean of all ipsilateral cortical ROIs of the same plane excluding the medial frontal ROI); for the medial frontal ROI, the metabolic index was calculated using the whole cortex mean CMRglu.

In addition to the cortical ROIs, one ROI was positioned over the area including the striatum and another over the thalamic area of the right hemisphere, and copied on the left side; these ROIs were positioned on plane III (plane OM + 58 mm of ECATII data, Case 4), because these anatomical structures are readily identifiable only on this plane (Kuhl *et al.*, 1982).

Statistical analysis

The patient data were compared with control values obtained in normal subjects using the same methods for PET scan and data analysis ($n = 13$ and $n = 6$ for the LETI and ECATII cameras, respectively) of similar age (40.5 ± 15.9 and 50.2 ± 10.0 yrs for the LETI and ECATII data, respectively, compared with 38 ± 17.8 yrs for the LETI patients, and 50 yrs for Case 4). The analysis first focused on individual data, by comparing each patient's values with the 95% confidence limits (CL) defined for each brain region from the control data, using the equation $CL = m \pm (t \times SD)$, where m is the mean control regional value, SD the standard deviation and t the student t value (two-tailed test, $n-1$ degree of freedom). Thus the calculation of the CL incorporates the small number of control values. This method enabled us to determine whether significant deviations from normality occurred for any brain region in each individual patient. Following this initial analysis, we also performed a comparison of mean regional data between patients and controls (exclusively on the LETI camera derived data, as only 1 patient was studied with the ECATII camera), using an analysis of variance.

CASE DESCRIPTIONS

Case 1 (see Laplane et al., 1984, Case 1)

V. was examined in our unit in 1980 when he was aged 53 yrs. Twelve years previously he had been stung by a wasp. This was followed by convulsions and then coma, which lasted several days. Before this he had been well, with no evidence of psychiatric symptoms. While recovering he had developed choreiform movements which had partially resolved, leaving some tic-like movements of the face and fingers. Gait was affected by a mixture of choreiform and parkinsonian-like disturbances. He had been considered to be demented, and would spend the day in a state of impassive inactivity, describing his own mental state as an 'empty mind'. His affect seemed normal when questioned about personal events, and there were no features of depression, but he reverted to his habitual state of indifference once left alone. Under stimulation he was able to perform complex tasks correctly (to play bridge, for example) and this was reflected by his performance on testing. Two years after the encephalopathy he began to develop stereotyped activities. The most frequent of these involved counting, often paced by finger movements. He would also spend long periods of time switching a light on and off. The fact that he would need to reach a certain multiple in his activities added to their compulsive character. 'C'est plus fort que moi', he would say. When interrupted he would become angry but not apparently anxious as such. On one occasion, when kicking a stone along a street, he experienced difficulty as a result of his gait disorder and, apparently unaware of the inappropriateness of his behaviour, went down on his knees and began to push the stone along with his hands, again in multiples.

Standard and sleep EEGs were normal. CT scans were performed in the orbitomeatal plane and slices were taken every 3 mm in the region of the basal ganglia. The lesions consisted of low density areas situated bilaterally in the internal part of the lentiform nucleus (fig. 2). The rostral part of the nucleus seemed to be more affected than its caudal part. Some other small low density areas could be seen rostrally within the right putamen and in the head of the right and the left caudate nuclei. Mild ventricular enlargement was present. The patient later died from the inhalation of food.

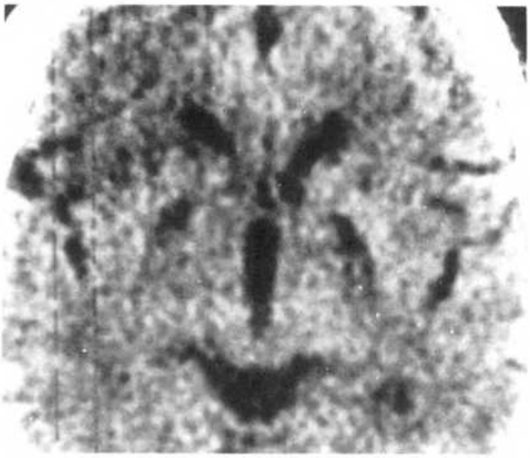

FIG. 2. *Case 1.* CT scan at basal ganglia level, in OM plane, showing small lesions in caudate and putamen and large bilateral lesions in the internal part of lenticular nuclei. (Left hemisphere is presented on the right side of the picture.)

Case 2 (see Laplane et al., 1984, Case 2)

D. was aged 23 yrs when he suffered from accidental carbon monoxide poisoning in 1979. There had been no evidence of previous psychiatric disorder. He was initially severely affected intellectually, but improved over the following months. Two years later there were no neurological signs. Intellectual performance was normal (Table 1), except for memory and verbal fluency. As with Case 1, however, there was an apparent lack of spontaneous activity, although he could be stimulated into action by his relatives. He also described his mental state as an 'empty mind' but showed no features of depression. His relatives were unaware of his stereotyped activities, which were purely mental. When alone, he would count to himself, but he was able to stop easily, without seeming to become anxious. There were no compulsive features in his personality. The EEG was normal. A CT scan (orbitomeatal plane, slice thickness 10 mm) showed 2 low density areas almost symmetrically placed in the internal part of the lentiform nuclei. There were no other abnormalities. The patient was lost to follow-up until 1987, when a neuropsychological assessment showed similar results. MRI revealed symmetric clearly defined abnormal signals in the globus pallidus bilaterally in their rostral halves, probably involving parts of both medial and lateral segments (fig. 3).

PET scan performed 8 yrs after the onset revealed regional CMRglu values within normal ranges. There was a significant decrease of 3 regional metabolic indices: mediofrontal on planes III and IV ($P < 0.02$ and $P < 0.05$, respectively) and left laterofrontal on plane IV ($P < 0.02$). There was also a significant increase in the lateral occipital metabolic index of plane III ($P < 0.05$).

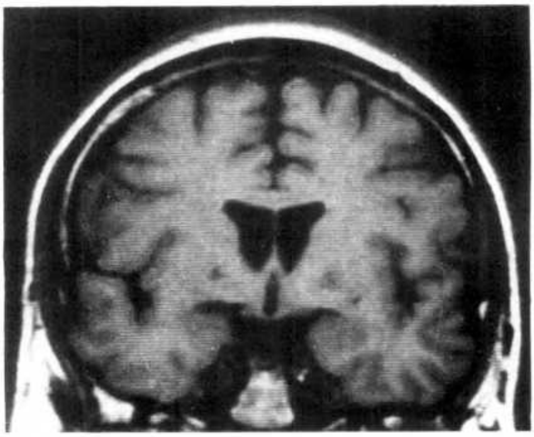

FIG. 3. *Case 2.* Bilateral pallidal damage on a coronal MRI slice (T1 weighted sequence).

Case 3 (see Laplane et al., 1984, Case 3)

P. was aged 59 yrs when, in 1970, he was accidentally poisoned by carbon monoxide. Other than his having lived alone with his mother and having never married, information concerning his past history was lacking. Following a brief period of coma, he suffered several days of headache and confusion. After recovering he tried to recommence his job as a messenger, but was dismissed because of slowness. Akinesia, extrapyramidal rigidity and reduction of verbal fluency were noted at that time, but there was improvement during the following years. Intellectual processes seemed slowed and there was an impression of mental deterioration, although he could perform complex tasks on request. The most striking feature was his passivity and lack of initiative, although his motor and mental capacities were largely preserved (Table 1). The interpretation of the apparent language disorder must be tempered by the fact that he was of Russian origin. He was institutionalized, spending most of his day inactive; he never attempted to leave hospital. His lack of initiative was not total, however, since he did from time to time help other patients to eat or shave, watch television, read a newspaper and so on. He was able to paint pictures, but for years he painted the same landscape. His affect was poor. The EEG was normal.

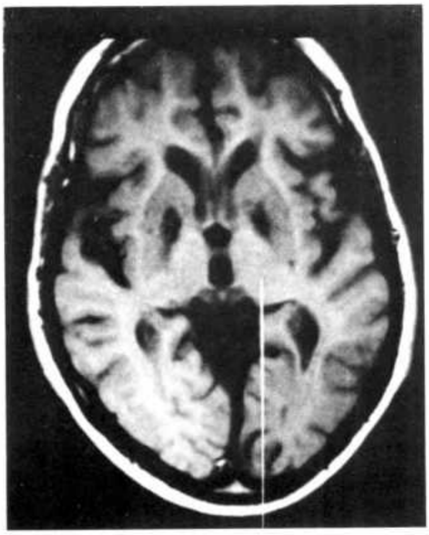

FIG. 4. *Case 3*. Bilateral calcified pallidal lesions on a horizontal MRI slice (T1 weighted sequence). Some degree of brain atrophy is present.

CT and MRI scans showed almost symmetric calcified lesions in the basal ganglia, occupying most of the region of the globus pallidus bilaterally (fig. 4). The dorsal parts of both pallidal segments seemed more affected, as seen on coronal sections, than the ventral segments. Cortical atrophy and ventricular enlargement were present.

The PET scan performed 14 yrs after the accident showed regional CMRglu values within the normal range. There was a significant decrease of the mediofrontal metabolic index on planes II, III, IV, V ($P < 0.02$, < 0.05, < 0.001, < 0.01, respectively), the right and left laterofrontal regions on plane II ($P < 0.01$ and < 0.02, respectively), the left laterofrontal region on plane IV ($P < 0.05$) and the right striatal region ($P < 0.01$). There were also significant increases of the metabolic indices in the right temporo-parieto-occipital area of plane III ($P < 0.001$) and in the left occipital area of plane III ($P < 0.01$).

Case 4

D., aged 52 yrs, was a former alcoholic who had been previously treated with disulfiram. Medical attention had been drawn to him because of his inactivity and lack of volition. He would lie in bed all day, and talked to no-one. If questioned, however, he would answer appropriately. He was not apparently bored with his lot, nor did he feel sad. His past history did not reveal any depressive or compulsive features. Neurological examination and EEG were normal.

CT scans (October 1984) showed bilateral low density areas visible on one slice (of 9 mm thickness) only. These lesions projected onto the pallidal areas. Unexpectedly, MRI abnormalities (5 months later, in March 1985) were less marked, with apparently a right-sided lesion only, involving parts of the putamen, of the lateral pallidal segment and of the head of the caudate nucleus (fig. 5). These lesions were attributed to intoxication by disulfiram which may have occurred several years previously.

The PET scan showed elevated rCMRglu values in all structures, but this increase reached statistical significance only in the lateral occipital cortex of both sides on plane III ($P < 0.02$). The left laterofrontal metabolic index on plane III was significantly decreased ($P < 0.05$).

Case 5

A. had at the age of 27 yrs suffered cerebral anoxia during general anaesthesia for appendicectomy. Before the accident she had been otherwise well. On recovery there was a pyramidal syndrome,

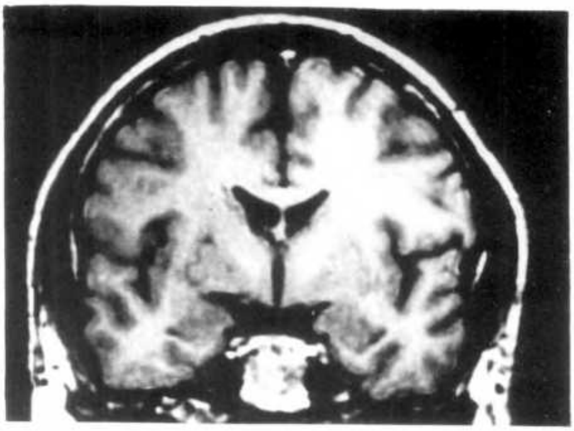

FIG. 5. *Case 4*. Right-sided lesion, probably due to disulfiram intoxication, involving parts of the putamen, of the lateral pallidal segment and probably of the caudate. This MRI section (coronal plane, T1 weighted sequence) showed less marked lesions than did the CT scan, where bilateral lucencies were present in the pallidal areas. CT scan was performed, however, six months earlier than MRI.

tremor, rigidity, and severe mental disturbance. Six years later, in contrast to her motor function, which had greatly improved, she was extremely inert. Housework was performed very slowly, and she would spend many hours doing nothing, sometimes in front of the television, in contrast to her premorbid behaviour. She felt sad, and was pessimistic about her future. In addition, she was subject to obsessive-compulsive behaviour. She was unable to restrain herself from timing her activities, and would schedule her tasks in detail. Some actions shared the features of a lack of inhibition of motor programs and those of compulsive behaviour. For instance, once when stirring soup, she was unable to stop spontaneously, and had to ask someone to immobilize her arm. The same phenomenon would occur if she began to scratch a part of her body.

The EEG was normal. CT scan and MRI showed small bilateral lesions within the lentiform nuclei. Although very narrow in the mediolateral dimension, they extended rostrocaudally along almost the whole of the globus pallidus, involving both the inner and outer segments (fig. 6). Frontal MRI slices were not obtained.

The PET scan performed 6 yrs after the onset showed no abnormality of the cortical CMRglu

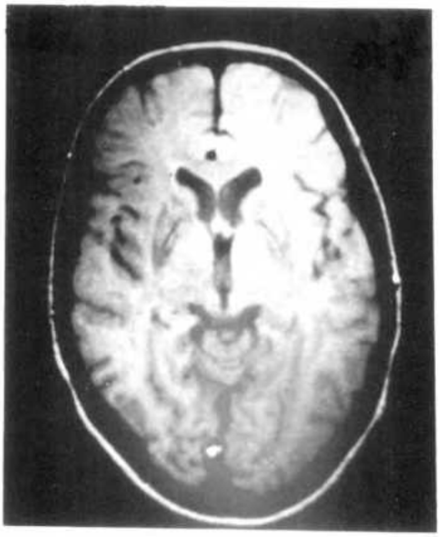

FIG. 6. *Case 5*. Horizontal MRI section (T1 weighted) showing abnormal signals in both pallidal areas.

values, but the striatal rCMRglu was significantly decreased on the right ($P < 0.02$). The metabolic indices were significantly decreased in the left laterofrontal area of plane IV ($P < 0.02$) as well as in both striatal regions ($P < 0.001$ and < 0.05 on the right and left sides, respectively).

Case 6

F. was examined by us in December 1985. Three years previously he had suffered an electric shock that had induced ventricular fibrillation followed by hypoxia and coma. He had been meticulous in his job as a clerk, but there had been no evidence of physical or psychological disturbance before the accident. Four months later, on return home from hospital, he was noted by his relatives to remain in bed until asked to rise, and would otherwise stay there. He seemed to take no initiative though he would perform tasks at the insistance of others. He showed a polymorphic compulsive behaviour. For instance, in walking down a corridor, he would feel obliged to turn on or off each light switch he encountered. He would walk on the pavement 'avoiding the lines'. He rechecked his behaviour constantly. In counting, he would avoid the number 13 and would often recite the alphabet. He did not seem to be disturbed by this behaviour and made no attempt to desist. He used to say that he was doing it 'pour rire'. If he was prevented from performing these acts, he would become angry, but not apparently fearful. Finally he had major memory difficulties which interfered with his daily life. Neurological examination and the EEG were normal. The neuropsychological examination is summarized in Table 1.

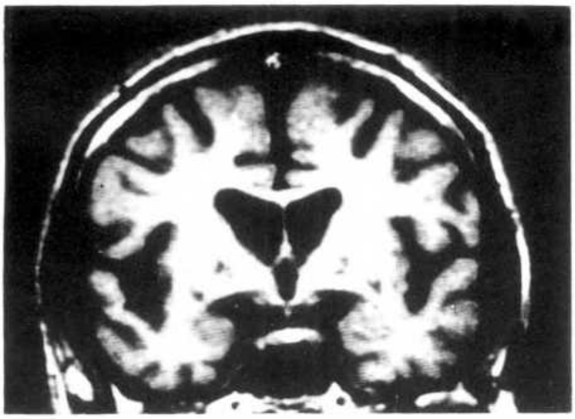

FIG. 7. *Case 6*. Frontal MRI section showing bilateral lesions which occupy predominantly the pallidum (dorsal part of medial segment) and the ventral part of the putamen (T1 weighted sections). Some degree of brain atrophy is present.

MRI showed almost symmetric bilateral lesions occupying the dorsal part of the globus pallidus, affecting mainly the lateral but also the medial segment (fig. 7). These lesions extended ventrally and laterally onto the two parts of the lentiform nucleus, pallidum and putamen, situated just above the lateral part of the anterior commissure. Some degree of cortical atrophy and ventricular enlargement was present.

The PET scan performed 2 yrs after the onset showed that the right striatal CMRglu value was significantly decreased ($P < 0.05$). No significant alteration of the metabolic indices was observed, although there was an increased mediofrontal CMRglu of planes III and IV which fell short of statistical significance.

Case 7

M., aged 31 yrs, was admitted because of unusual neuropsychiatric sequelae of self-induced carbon monoxide poisoning. Her past history had included, since the age of 15 yrs, depressive periods with suicide attempts, drug abuse, and alcoholism. Her marriage had failed and she had continued her life as a homosexual. Her personality had been considered to be psychopathic and

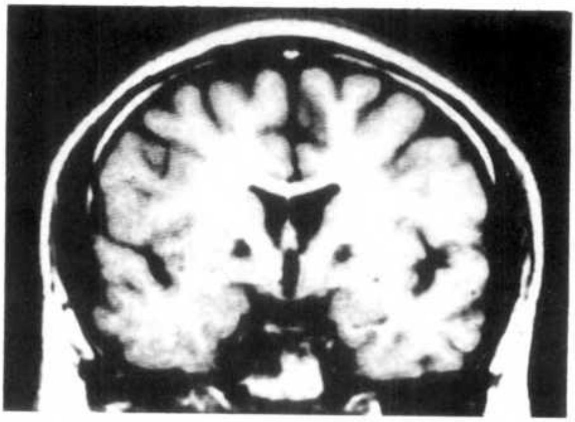

FIG. 8. *Case 7.* Frontal MRI section (T1 weighted sequence) showing symmetric clear-cut abnormal signals which project upon the rostral and dorsal parts of the globus pallidus.

impulsive by psychiatrists at the time. In 1983, following accidental carbon monoxide intoxication, she began to exhibit new compulsive activities. Three types of behaviour were noteworthy. She would repeatedly look at her watch and repeat the time to herself. She would count in her mind the number of words spoken by another person, and if the total was not a multiple of three, she would add words. This habit usually induced a delay before she was ready to answer any question posed. The third type of compulsion consisted of the repetition of a mandatory sentence, according to the action in progress: 'Je n'ai pas fait cela pour rien' when finishing a cigarette, or 'Ceci appartient au passé' before drinking. In spite of the fact that she was well aware of the absurdity of these actions, she could not restrain herself from performing them. When she attempted to fight against them, she would at once experience anxiety and a compulsion to execute the action. A general slowing was noted, partly explained by the time demanded by some of her compulsions. Neurological examination was otherwise normal.

CT and MRI scans showed bilateral, well-delineated lesions of the lentiform nuclei (fig. 8). These lesions involved the anterior part of the globus pallidus, from the anterior commissure rostrally, as far as the anterior thalamic nuclei caudally, leaving unaffected the posterior and ventral parts of the nucleus. Lesions were primarily located in the lateral pallidal segment, although a part of the medial segment was also probably involved. This lesion, as evaluated from the MRI data, occupied approximately one-quarter of the volume of the globus pallidus. Lesions were roughly symmetric, although slightly more rostral on the left. A slight encroachment on the anterior limb of internal capsule could not be excluded.

The PET scan performed 3 yrs after the event showed no significant abnormality of rCMRglu values. With respect to the metabolic indices, they significantly decreased in the mediofrontal area of plane IV ($P < 0.05$), the right laterofrontal area on plane V ($P < 0.05$), the left laterofrontal area of plane II ($P < 0.05$) and the right striatal area ($P < 0.05$). In addition, the metabolic index of the left latero-occipital area of plane III was significantly increased ($P < 0.01$).

Case 8

K., a 22-yr-old, previously well, north African woman, was admitted to the intensive care unit at the Hôpital Beaujon unresponsive and stuporose following accidental carbon monoxide intoxication. The initial CT scan performed 2 days later showed bilaterally symmetric lucencies in in the region of the internal segment of the globus pallidus. After progressive return of normal consciousness, marked psychomotor inertia remained. Whereas her family noted no intellectual deterioration, a formal neuropsychological assessment was not possible because of language difficulties. Her condition remained apparently unchanged for the next 2 months, when MRI and PET scans were performed. No obsessive or compulsive features were noted.

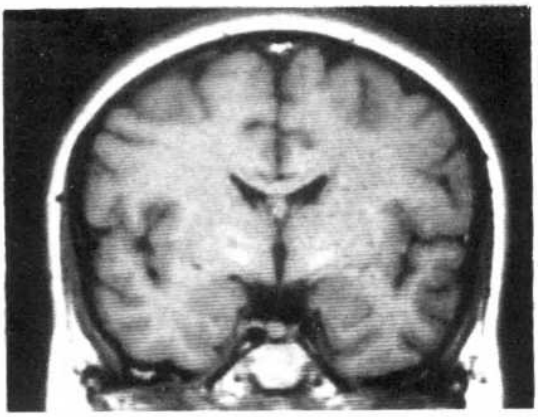

FIG. 9. *Case 8*. Frontal MRI shows symmetrically abnormal signals in the internal segment of the globus pallidus bilaterally (increased signal on T1 sequence).

The MRI scan showed symmetric punctate abnormal signals in internal globus pallidus segments bilaterally (hypersignals on both T1 and T2 sequences). No lesions were seen elsewhere, and no significant cortical or subcortical atrophy was noted (fig. 9). In spite of the lack of full neuropsychological assessment, this patient is included in the present series because it was possible to obtain a PET scan.

The PET scan, performed 2 months after the accident, showed that the rCMRglu (plane IV was unavailable) values were low throughout but this decrease reached statistical significance only in both striatal areas ($P < 0.01$ and 0.05 on the right and left, respectively). The metabolic indices of the right and left laterofrontal areas of plane III were significantly decreased ($P < 0.01$ and 0.05, respectively) as well as of the right striatal area ($P < 0.02$). There were significant increases of the metabolic indices in the right laterotemporal area of plane III ($P < 0.02$) as well as in both latero-occipital areas of plane III ($P < 0.02$ on the right and 0.001 on the left).

RESULTS

Neuropsychological assessment

The main results of neuropsychological testing are given for each patient (except Case 8 who was not testable) in Table 1. In spite of some degree of interpatient variability, several common features were present. (1) Intellectual function remained within normal limits in most of the patients, although performance might have been affected by variability of attention. Learning was disturbed in Cases 2 and 6. (2) Linguistic and gestural specific activities, calculation and drawing were intact. (3) Orientation in space and time was preserved. (4) Recall of early-acquired general knowledge and of old or recent personal memories was correct, except in Cases 2 and 6, providing appropriate questions were asked of the patients. (5) Spontaneous activity was very restricted, but it improved greatly with stimulation by the examiner. (6) Cognitive slowing, although it consistently affected daily living, varied during examination from one patient to another, and sometimes from one test to another in the same patient. (7) Reduced digit span, forwards and backwards, and unexpected exhaustion or variability of performances in some tests, revealed attention disorders. (8) Mental control subtests using patterned

TABLE 1. NEUROPSYCHOLOGICAL RESULTS*

	Case						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Age (yrs)	52	26	70	50	33	36	31
Education (yrs)	15	12	10	8	12	10	8
WAIS verbal IQ	103	116	80	93	108	79	88
Raven's PM 38 IQ	114	99	100	111	108	85	99
Wechsler Memory Scale							
MQ	91	70	97	100	108	57	98
Mental control	9	9	4	7	8	4	8
Digits forward	5	6	3	6	6	4	7
Digits backward	3	3	2	4	4	2	3
Logical memory A	9	2	10	11	22	1	18
Logical memory B	7	2	7	9	14	1	4
Wisconsin Card Sorting test							
Categories	5	4	0	2	6	1	2
Perseverations	9	8	10	1	0	10	0
Verbal fluency (60 s)							
Animals	12	12	4	20	14	14	9
Words beginning with M		2	1	1	14	1	3
Perturbation in motor series	+	+	+	+	+	+	–
Rey Complex Figure							
Copy	Details	Rectangle	Rectangle	Rectangle	Rectangle	Details	Rectangle
Memory reproduction	Details	Rectangle	Details	Details	Details	Details	Rectangle
Fifteen objects tests (time)				150 s	22 s		30 s
Specific difficulties	Writing disorders	Micrographia	Micrographia	Micrographia	Writing disorders	Attention disorders	Variability
Depression and anxiety	–	–	–	–	+	–	+

* Case 8 was not testable.

learned material were relatively well performed. (9) Verbal fluency for words of the same semantic category (animals) was normal for most of the patients. (10) The listing of words beginning with M (which required more innovation and thought), was poor. (11) Some patients had problems extracting a structure from the Rey-Osterrieth complex figure. (12) Tests of reproduction of the same figure from memory indicated that attention was directed either towards the large central rectangle or towards the details, but that the overall synthesis was never performed. (13) The elaboration of a new strategy, the shifting of attitude in order to adapt to a changing situation, and the sequential programming of activity were also disturbed, as shown by the Wisconsin Card Sorting test, Luria's arithmetic problems or graphic and motor series. (14) No abnormal imitation, prehension, or utilization behaviour was observed during testing, but for Case 6 the family reported compulsive utilization behaviour at home. (15) Refusal behaviour was never observed by investigators, but motivation decreased quickly in the face of difficulty or lack of success. (16) Personality, as evaluated by the MMPI, was preserved, but affect was severely impaired. In 2 patients a depressive condition was noted. It appeared before the brain damage in one, and afterwards in the case of the other.

Neurological examination

In contrast to the significant neuropsychological abnormalities seen in the patients, relatively few neurological physical signs were exhibited. Three patients had a mild parkinsonian-like syndrome, 1 of whom had tic-like movements; the other 5 had a normal neurological examination.

Summary of PET findings

1. The cortical *CMRglu values* were unremarkable, if Case 4, in whom the occipital metabolism was significantly elevated, is excluded. In the striatal area, however, the CMRglu was significantly reduced in 3/7 cases, while no changes were seen in the thalamic area.

2. The analysis of individual *cortical metabolic indices* was remarkable in the following respects. (1) The occurrence of significantly abnormal values (23 out of 185 analysed regional values or 12%) was higher than expected by chance alone. (2) Among the 23/185 significantly abnormal areas, 16 were frontal cortex areas (out of a total of 75 frontal cortex values) and 7 nonfrontal areas (out of 110 nonfrontal areas), a statistically significant distribution ($\chi^2 = 9.19$, $P < 0.01$). (3) Each of the 16 significant decreases were located within the frontal lobe, while each of the 7 significant increases were outside the frontal cortex, a distribution statistically significant by χ^2 ($\chi^2 = 18.94$, $P < 0.01$) (*see* fig. 10).

Among the 7 patients studied, 6 individually demonstrated at least one significantly decreased regional value in the frontal lobe, of whom 4 also showed a significantly increased index in nonfrontal posterior cortex. Among the 16 abnormally low frontal indices, 7 were located in the medial frontal cortex, 7 in

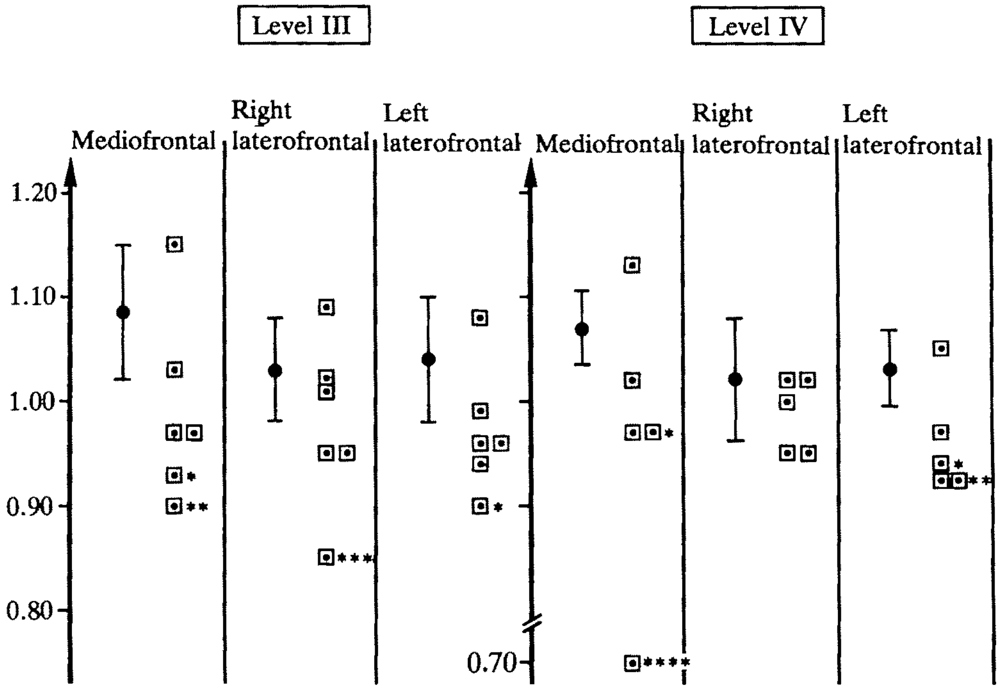

FIG. 10. Individual frontal metabolic indices (frontal CMRglu/mean cortical CMRglu, closed circles in squares), calculated separately for brain levels III and IV and for 3 regions (the mediofrontal and the right and left laterofrontal areas) in the 6 patients studied on the LETI camera (Cases 2, 3, 5, 6, 7 and 8; level IV was unavailable in Case 8). The mean (±1 SD) corresponding values in control subjects are also shown (closed circles). *$P < 0.05$; **$P < 0.02$; ***$P < 0.01$; ****$P < 0.001$.

the lateral prefrontal cortex, and 2 in the laterobasal frontal cortex, without any noticeable clustering either among these 3 anatomofunctional subdivisions, or in the vertical (axial) direction. Of the 7 significant increases in nonfrontal cortex metabolic indices, 5 were located in the occipital area and 1 each in the temporal and the temporo-parieto-occipital cortices.

3. *Subcortical metabolic indices.* Among the 14 striatal metabolic indices, 6 were significantly abnormally low and none abnormally high; these changes occurred in 4 of the 7 patients. No significant abnormality was found in the analysis of the thalamic metabolic indices.

For illustration, fig. 11 depicts the CMRglu images (plane III) of each of the 6 patients investigated with the LETI camera (Cases 2, 3, 5-8), as well as for a typical control subject.

Mean regional metabolic data

Table 2 shows the *mean rCMRglu* and the *mean regional metabolic indices* for all cortical areas analysed (after combining the right and left original cortical regions as the individual results did not show any trend for lateralized metabolic

TABLE 2. MEAN (±1 SD) REGIONAL CORTICAL GLUCOSE UTILIZATION (rCMRglu) AND CORRESPONDING METABOLIC INDICES IN 6 PATIENTS AS COMPARED WITH 13 CONTROL SUBJECTS

	Cortical area																
	Mediofrontal				*Laterofrontal*				*Temporal*			*Parietal*	*Temporo-occipital*		*Parieto-occipital*	*Occipital*	
Level[a]	*II*	*III*	*IV*	*V*	*II*	*III*	*IV*	*V*	*II*	*III*	*IV*	*V*	*III*	*IV*	*V*	*III*	*IV*
Controls[c]																	
rCMRglu	6.86	6.81	6.68	7.14	6.24	6.48	6.45	6.90	5.43	6.74	6.24	6.65	5.50	5.90	6.60	6.31	6.77
(mg/100 g/min)	±1.66	±1.48	±1.22	±1.80	±1.29	±1.38	±1.39	±1.60	±0.97	±1.18	±1.47	±1.58	±0.95	±1.20	±1.45	±1.02	±1.13
Metabolic	1.078	1.086	1.067	1.051	0.991	1.036	1.027	1.026	0.868	1.083	0.994	0.987	0.885	0.941	0.983	1.018	1.086
index[b]	±0.091	±0.062	±0.035	±0.086	±0.055	±0.049	±0.056	±0.043	±0.060	±0.045	±0.088	±0.048	±0.033	±0.054	±0.037	±0.068	±0.067
Patients[d]																	
rCMRglu	5.90	5.70	5.65	5.64	5.59	5.72	6.11	5.95	5.21	6.56	6.30	6.08	5.58	5.88	6.14	6.94	7.34
(mg/100 g/min)	±1.34	±0.88	±1.03	±1.00	±0.91	±1.13	±0.61	±1.49	±0.68	±0.90	±1.09	±1.02	±1.32	±0.80	±1.47	±0.88	±1.13
Metabolic	0.994	0.992**	0.992	0.953	0.910**	0.975*	0.976*	0.995	0.875	1.085	1.000	0.986	0.912	0.938	1.013	1.155†	1.133
index[b]	±0.143	±0.089	±0.164	±0.146	±0.065	±0.067	±0.038	±0.040	±0.069	±0.067	±0.066	±0.042	±0.077	±0.030	±0.045	±0.121	±0.062

[a] Brain level of PET scan, *see* fig. 1. [b] Calculated as regional cortical CMRglu/mean cortical CMRglu of same level (*see* Methods). [c] n = 13 subjects, but mean regional values based on 10–13 individual data because of occasional unavailability of 1 PET level. [d] n = 6 patients, but mean regional values based on 4–6 individual data (*see* [c]). * Significant decrease (* $P < 0.05$, ** $P < 0.02$), relative to controls by ANOVA. † Significant increase ($P < 0.01$) relative to controls by ANOVA.

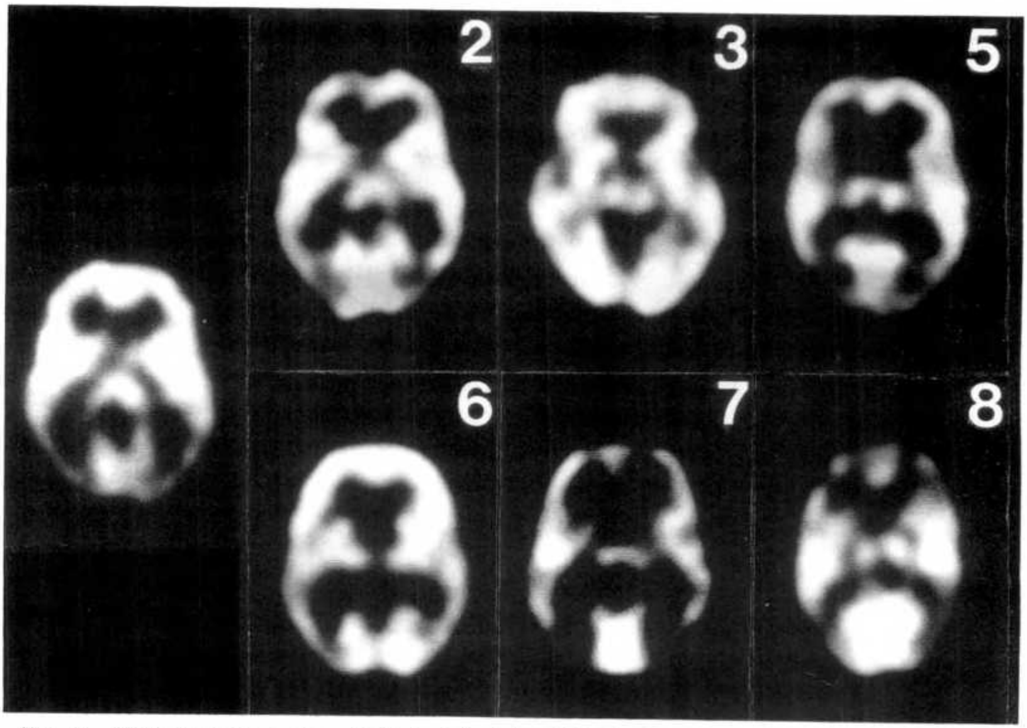

FIG. 11. PET images representing rCMRglu at brain level III (the 'basal ganglia cut') obtained in 1 control subject (on image at bottom of fig.) and in 6 patients (2, 3, 5, 6, 7, 8) studied with the LETI camera. In these images, anterior is uppermost and right is to the left; whiter shades of grey indicate higher metabolism. These images are not cross-scaled, so that differences in mean metabolic rate among patients are not apparent; this mode of display, however, allows visual assessment of the regional metabolic pattern. Compared with the control subject, whose image is typically normal, there is a mild degree of relative prefrontal cortex hypometabolism in all patients except Case 6; this effect was statistically significant on this brain level in Cases 2, 3, 8, and at a different brain level (not shown) in Cases 5, 7 (*see* PET results section 'Individual data analysis').

TABLE 3. MEAN (±1 SD) REGIONAL SUBCORTICAL rCMRglu AND CORRESPONDING METABOLIC INDICES IN 6 PATIENTS COMPARED WITH 13 CONTROL SUBJECTS

	Subcortical area	
	Striatal	*Thalamic*
Controls[c]		
rCMRglu (mg/100 g/min)	6.85	6.31
	±1.13	±1.01
Metabolic index[b]	1.107	1.018
	±0.098	±0.093
Patients[d]		
rCMRglu (mg/100 g/min)	5.05***	5.82
	±1.02	±0.76
Metabolic index[b]	0.881****	0.950
	±0.098	±0.045

[b, c, d] *see* Table 1. Asterisks = significantly decreased relative to controls by ANOVA ***$P < 0.01$, ****$P < 0.001$.

effects). There was no significant abnormality of *mean rCMRglu values* although there was a trend for decreased rCMRglu in most frontal cortex areas. Of the 8 frontal regions analysed, 4 showed a significantly depressed *metabolic index* (the laterofrontal cortex of planes II, III, and IV and the mediofrontal cortex of plane III ($P < 0.02$, < 0.05, < 0.05 and < 0.02, respectively). In addition, the mean metabolic index in the occipital cortex was significantly increased ($P < 0.01$).

Table 3 shows the mean rCMRglu and the mean metabolic indices for *subcortical areas*. In the striatal region, both the CMRglu and the regional metabolic index were significantly decreased ($P < 0.01$ and 0.001, respectively). There were no significant changes in the thalamic areas.

DISCUSSION

Relationship to the frontal syndrome

Clinical studies

The first feature of note is the similarity of this syndrome to the frontal lobe syndrome, although here the lesions are at basal ganglia level, in the lentiform nuclei. It is difficult to find a neuropsychological definition of the frontal syndrome which is accepted by all authors. Several features are, however, considered as characteristic. Among the most significant is the loss of drive. All our patients had a decrease in spontaneous activity and drive. This was very marked in all patients except Cases 3 and 7 and was readily reversible under stimulation by the patients' relatives and friends. This is also the case with 'frontal' patients (Stuss and Benson, 1986). Consequently, this sign can be masked under test conditions. As emphasized by Eslinger and Damasio (1985), these disorders are more marked in day to day life than in artificial situations such as the neuropsychological examination. The decrease in verbal fluency is also frequently encountered in the 'frontal' syndrome. The finding of words belonging to a given semantic group was less altered than the listing of words beginning with a given letter. Such a dissociation has also been described in the 'frontal' syndrome (Stuss and Benson, 1986). Attention disorder, another frontal sign, was also present although less marked in our patients. Memory disturbances were marked in 2 patients (Cases 2 and 6). In Case 6, amnesia was a part of a global deterioration of cognitive function, suggesting the possibility of more diffuse lesions.

Responses to the Wisconsin Card Sorting test, often thought as the most sensitive test of frontal dysfunction, were markedly abnormal in most of our patients, and especially in Cases 3 and 7. They were, however, normal in Case 5. Qualitatively, results varied. Some of the patients exhibited severe perseverations, whilst others (Cases 1, 7) showed better control, perhaps because they had better insight into their disorder. Visuoconstructive tests primarily revealed difficulties in understanding an image pattern as a whole. Finally, the presence of affective disorder needs discussion. Patients showed a lack of concern regarding their own problems and those of their relatives. The absence of foresight suppressed anxiety.

Here also the severity of the disorder was variable, since for Cases 5 and 6, affect was not completely lost, and depressive thoughts and anxiety were present. The neuropsychological findings are thus similar to those observed following frontal lobe damage. The question arises as to whether there were frontal lobe lesions, associated with basal ganglia damage, but unidentified on morphological imaging of the brain.

From a clinical point of view, frontal-like syndromes have been described in basal ganglia disorders such as progressive supranuclear palsy (Cambier *et al.*, 1985) and Parkinson's disease (Taylor *et al.*, 1986; Gotham *et al.*, 1988). The present observations of frontal-like syndromes with bilateral lesions of the lentiform nuclei are more suggestive of this relationship since motor dysfunction, which sometimes complicates the interpretation of neuropsychological testing in the above mentioned diseases was, in our cases, absent or only mild.

PET studies

The PET studies, performed in 7 of the 8 patients reported here, revealed several noteworthy findings. First, there was evidence of unilaterally or bilaterally decreased striatal glucose utilization (absolute values and/or relative metabolic indices), in 5/7 patients. Secondly, the glucose utilization values in the cerebral cortex were essentially normal, as compared with control subjects of similar age. Thirdly, despite this lack of significant alteration in cortical rCMRglu, there was a significant reduction in glucose utilization in various parts of the frontal cortex *relative* to the whole cortex in 6/7 patients taken individually, as well as in 4/8 frontal cortex subdivisions (namely, two laterofrontal, one latero-fronto-basal and one mediofrontal area) when the whole group of patients was analysed; as a corollary to this relative prefrontal cortex hypometabolism, there existed a significant *relative* hypermetabolism of the occipital cortex in several patients individually, as well as on average in the whole sample. These results establish the occurrence in our patient sample of an imbalance between anterior and posterior cortex glucose use, resulting in an altered anteroposterior gradient of cortical metabolism, which will be referred to in what follows as a *relative prefrontal hypometabolism.*

The reduced glucose use in our 'striatal' areas presumably reflects the inclusion, within our ROIs, of the damaged part of the lentiform nucleus; due to the relatively low spatial resolution of our PET device, this damaged area could not be directly visualized, and in turn, could not have been excluded in the regional data sampling procedure (*see* fig. 1). It remains possible, however, that part of this striatal hypometabolism represents a remote effect of the actual lesion, for example, as a result of retrograde dysfunction along striatopallidal pathways.

The relative prefrontal hypometabolism found in our patients may be due to several mechanisms: a morphologically detectable loss of cerebral tissue, a neuronal loss without gross morphological alteration, or a deafferentation process.

A morphological loss of frontal cortex tissue is an unlikely explanation for this finding because all 5 patients in our group who did not show clear-cut cortical atrophy on the MRI scan had a significant relative prefrontal hypometabolism, while only 1 (Case 3) of the 2 patients with a substantial cortical (not especially frontal) atrophy exhibited this finding. Lesions of the white matter of the centrum semiovale are known to occur in some instances of anoxic encephalopathy (Lapresle and Fardeau, 1966; Ginsberg, 1985) and could possibly, if present, disconnect the frontal cortex; however, no significant abnormality of the MRI white matter signals was observed in our patients.

Two of our patients (Cases 4, 7) were former alcoholics, a condition associated with relative mediofrontal hypometabolism of unclear mechanism (Samson *et al.*, 1986); however, the relative prefrontal hypometabolism present in both was localized to the mediofrontal cortex in only 1 of these 2 cases (Case 7).

A microscopic neuronal loss in the frontal cortex without gross structural damage cannot be formally excluded as in none of our patients was histological examination available. Published detailed accounts of neuropathology in 22 cases of carbon monoxide encephalopathy, however, showed (in those dying later than 10 days after encephalopathy) no cortical damage in 5/9, minor cortical damage in 3/9 and noticeable damage in only 1/9; in addition, it is not indicated in this report that these scanty cortical lesions predominate in the frontal cortex (Lapresle and Fardeau, 1967). In the neuropathological study of one case of carbon monoxide poisoning, Kobayashi *et al.* (1984) indicated that 'the cytoarchitecture of the frontal cortex was unremarkable'. Similarly, damage to the cerebral cortex was not a feature in the detailed pathological study performed by Ginsberg *et al.* (1974) in 14 monkeys following experimental carbon monoxide intoxication. On the whole, therefore, although it is difficult to exclude the possibility that neuronal damage concentrated in the frontal cortex could have contributed to the observed metabolic abnormality, particularly in some of our cases, the radiological data as well as the neuropathological literature suggest it could hardly explain the consistency of our observation across 6 subjects of our sample. We would therefore favour a process of deafferentation of the prefrontal cortex to explain our findings, as a result of bilateral lesions in the area of the globus pallidus.

Such a mechanism has been generally implicated to explain the depression of glucose utilization and oxygen consumption in the cerebral cortex following subcortical lesions in other grey matter nuclei (Feeney and Baron, 1986; Perani *et al.*, 1987). Thalamic lesions of vascular or surgical origin often result in diffuse ipsilateral cortex hypometabolism which apparently underlies the neuropsychological impairment and has been ascribed to damage to the thalamocortical projection system (Baron *et al.*, 1986). Following stereotactic lesions of the nucleus basalis of Meynert in the baboon, there is a marked ipsilateral, predominantly frontal, cortical reduction of glucose utilization which is linearly correlated with the extent of cortical cholinergic deafferentation as measured by choline acetyl transferase activity (Kiyosawa *et al.*, 1987). In patients with large left putaminal haemorrhage, Metter *et al.* (1986) observed temporal cortex hypometabolism which was proportional to the severity of aphasic symptoms. Finally, symptomatic Wilson's disease results in a marked but diffuse reduction in cortical glucose utilization (Hawkins *et al.*, 1987), in the development of which extralenticular pathology, especially cortical lesions, may however play a role.

This is the first report of cerebral glucose utilization in patients with bilateral lentiform lesions affecting predominantly or exclusively the globus pallidus. We are not aware of experimental bipallidal lesions studied with ^{14}C-deoxyglucose autoradiography. Although the lesions in some of our patients also affected part of the putamen, it is interesting to note that striatal lesions in rats do not result in significant frontal cortex hypometabolism (Kelly *et al.*, 1982; Kelly and McCulloch, 1984), suggesting that our findings in patients can probably be specifically ascribed to the pallidal lesions (it is possible, though, that any subpallidal extension of the lesion would have encroached upon the area innominata, and particularly the nucleus of Meynert, but the damage in our cases apparently spared this area). The only example of a pathological entity studied by PET which consistently involves the globus pallidus bilaterally, is progressive supranuclear palsy (PSP), where a conspicuous prefrontal cortex hypometabolism has repeatedly been demonstrated (D'Antona *et al.*, 1985; Leenders *et al.*, 1988) (although lesions of other systems are present in this degenerative disorder). The pathways linking the globus pallidus to the prefrontal cortex that would most likely be implicated in the development of the frontal dysfunction are the pallido-thalamo-cortical systems (*see* below); the process of prefrontal deafferentation in this case would therefore occur on a transneuronal basis.

It is tempting to implicate the observed frontal hypometabolism in the behavioural expression of bilateral pallidal lesions, which, by itself, is suggestive of dysfunction of the frontal cortex (*see* earlier discussion). Similarly, the intellectual impairment typical of PSP is characteristic of the frontal lobe syndrome and, as discussed above, is associated with a marked prefrontal hypometabolism. We searched for correlations between our frontal metabolic indices and the type and severity of the behavioural symptoms: there was no association between obsessive-compulsive features and/or psychic inertia on the one hand and the occurrence of significant frontal cortex hypometabolism and its topography within the frontal lobe on the other. For example, Baxter *et al.* (1987) recently reported a significantly increased glucose utilization in the left orbitofrontal cortex in obsessive-compulsive disorder. In addition to its small sample size, our study is made more difficult by the variability produced by the differing mechanisms of initial damage, ages of onset, and extensions of extrapallidal damage (Cases 3 and 6 had conspicuous cortical atrophy, and several cases showed putaminal damage).

At first sight, the dissociation between the severity of the behavioural impairment in our patients and the mildness of the metabolic changes, which affected the relative metabolic indices of the frontal lobe, may seem surprising. One hypothesis would be that the dysfunction of the cortical neurons, although present, had little consequence on the overall measured glucose utilization, because different neuronal populations are affected in opposite ways or because the neurotransmitter imbalance may not have disturbed the ionic gradients; a similar mechanism may explain the lack of significant cortical glucose hypometabolism in the dementia of Huntington's disease (although a slight relative frontal hypometabolism may be present in advanced cases; *see* Kuhl *et al.*, 1982; Young *et al.*, 1986). Alternatively, the significant prefrontal metabolic depression found here, although small, may nevertheless reflect a major disruption in the normal functional relationships between the prefrontal cortex and other interconnected cortical fields as well as with subcortical nuclei (Goldman-Rakic, 1987*a*) and, in turn, in a balance fundamental for normal behaviour. A similar rationalization would apply to the repeated observation of frontal cortex hypometabolism in patients with schizophrenic disorders (for review, *see* Buchsbaum, 1987). It is also possible that bipallidal lesions initially induce much larger effects on cerebral cortex metabolism, but that, as occurs in unilateral thalamic lesions, a progressive almost complete recovery occurs thereafter (Cambon *et al.*, 1987), in parallel with the clinical recovery. This would be consistent with the fact that the lowest CMRglu values were observed in the patient studied the earliest following the anoxic episode (2 months, Case 8). The recovery of clinical impairment, however, appears limited in bipallidal lesions.

On the other hand, it must be emphasized that the lack of significant reduction in cortical CMRglu in our patients is consistent with the overall preservation of global intellectual function. For example, the relative prefrontal cortex hypometabolism, characteristic of the 'subcortical' dementia of PSP, is actually superimposed on a significant depression of glucose utilization throughout the whole cortical mantle (D'Antona *et al.*, 1985; Leenders *et al.*, 1988): while the former may underlie the specific frontal lobe symptoms, the latter may be a counterpart to the global intellectual impairment found in this disease.

The prefrontal-basal ganglia-thalamocortical pathways

There have been conspicuous advances in the understanding of the anatomical relations between the basal ganglia and frontal associative cortex over the past decade. Recent anatomical and physiological findings have reinforced the general principle that some basal ganglia influences are transmitted only to restricted portions of the frontal lobe. Several segregated basal ganglia-thalamocortical pathways can be described, each of them including discrete, essentially nonoverlapping parts of neostriatum, pallidum or substantia nigra, ventral thalamus and cortex (Alexander *et al.*, 1986; Nauta, 1986). The 'motor' circuit, whose cortical target is the supplementary motor area, is the best documented from an anatomical and functional point of view, but the 'association' circuits are likely to be the anatomical basis of our patients' disorders. A dorsolateral prefrontal circuit has been proposed. The neostriatal input terminates within the dorsolateral head of the caudate and throughout a continuous rostrocaudal expanse that extends to the tail of the caudate (Yeterian and Van Hoesen, 1978; Selemon and Goldman-Rakic, 1985). These specific sectors of caudate nucleus project to the globus pallidus and to rostral portions of the substantia nigra. With respect to the globus pallidus, several experimental studies indicate that the 'association' sectors correspond to rostral, medial and dorsal parts of the nucleus (Parent *et al.*, 1984; Percheron *et al.*, 1984). The pallidothalamic input of this association circuit terminates in the different parts of the ventral anterior and mediodorsal nuclei of the thalamus. Another circuit terminates in the lateral orbitofrontal cortex. It includes a ventromedial sector of the caudate nucleus and a dorsomedial sector of internal pallidal segment. The limbic circuit, which has been previously described and which includes the ventral striopallidal system (Heimer and Van Hoesen, 1979), could also be implicated.

It should be emphasized that the functional correlations are rather well documented for the motor circuits, but not yet for the associative circuits. It has been shown that bilateral lesions in primates restricted either to the lateral orbitofrontal area or to the portions of the caudate to which it projects appear to result in a perseverative interference with an animal's capacity to make appropriate switches in behavioural set (Divac *et al.*, 1967; Mishkin and Manning, 1978).

There was, however, an associated involvement of the motor systems channelled by the globus pallidus in some of our patients. Cases 1, 2 and 5 presented in milder degree the same extrapyramidal symptoms as those reported in the literature in cases of pallidal damage (Grinker, 1926; van Bogaert, 1946; Martin, 1965; Klawans *et al.*, 1982; Jellinger, 1986).

The anatomicoclinical correlations of these observations present further difficulties due to the fact that brain lesions of similar location may induce neuropsychological disorders that are somewhat variable from one patient to another, as shown in Table 1. For instance, in Case 3 spontaneous activity was relatively preserved but performance on the Wisconsin Card Sorting test was very poor, verbal fluency was altered, affect was decreased, and anxiety and depression were absent. In contrast, in Case 5, activity was dramatically reduced, performance on the Wisconsin Card Sorting test was normal, verbal fluency was intact and strong anxiety and depressive elements were present. In spite of the fact that all the case reports shared the same global pattern, a detailed analysis reveals obvious differences. These facts might be explained by the modular organization of the frontal cortex and by the interdigitation of these modules (Goldman-Rakic, 1987*b*). According to this functional concept, a slight displacement of the lesion could produce a change in the modules under stimulation, and thus induce different disorders.

Relationships with psychiatric diseases

It is certain that the inertia, akinesia, and slowness seen in major depressive conditions can closely resemble the frontal-like syndrome following lesions of the lentiform nuclei. Some of our patients, in fact, were thought for a time to be depressed and diagnostic confusion between certain frontal syndromes and depressive states is well known. The strict application of the DSM III criteria without taking into account all clinical aspects may lead to such errors. The principal difference between our patients (and, by extension, all cases with frontal syndromes) and depressed patients is the subjective absence of sadness and of anxiety. The clinical impression of similarity between depressive states and 'lenticular' syndromes is reinforced by some metabolic PET studies which have shown, in endogenous depression, the existence of hypometabolism predominantly in the frontal region of the left hemisphere which disappears as the patient improves (Phelps *et al.*, 1984). Equally, the similarities between negative forms of schizophrenia and frontal syndrome have been underlined in the literature, and PET studies have confirmed the existence of frontal hypometabolism in cases of schizophrenia, in spite of occasional contradictory evidence (*see* Buchsbaum, 1987, for a review). The existence of obsessive-compulsive disorders, however, constitutes the most novel of our observations, although it must be noticed that not all our patients exhibited these. The occurrence of such abnormal behaviour after basal ganglia damage has already been reported amongst the sequelae of encephalitis lethargica (Jeliffe, 1929) and in Parkinson's disease (Schwab *et al.*, 1951). Furthermore, the obsessive aspects of some activities in Gilles de la Tourette syndrome are well known (Frankel *et al.*, 1986) and several arguments support the hypothesis of basal ganglia lesions in this disease (Devinski, 1983). In spite of the similarities between our patients' lesions, not all displayed such behaviour. The behavioural disorder was marked in Cases 1, 5, 6, 7 and in the 2 cases of Ali-Cherif *et al.* (1984), and fitted the DSM III definition of obsessions and compulsions. In Case 2 it consisted of simple mental stereotypies, without compulsive characteristics. Case 1, moreover, displayed abnormal movements very similar to those observed in Gilles de la Tourette syndrome. Case 5 also showed abnormal movements which were remarkable, in that once started, she was unable to stop a repeated movement unaided. In this latter case, the disorder might be attributed to a lack of motor program inhibition, as described by Luria (1965) in 'frontal' patients whose lesions extended to the basal ganglia. In our observations, it would seem that patients were unable to inhibit some programs that were either purely mental or both motor and mental. There seems to be in this series of patients a continuity between the motor stereotypies, some resembling tics, the mental stereotypies, and the obsessive-compulsive behaviours proper. Since motor stereotypies can be clearly related to basal ganglia disorder, this continuity represents an additional argument for attributing the behavioural syndrome to the lentiform nucleus lesions and not to other lesions undetectable on available imaging techniques. Finally it is worthy of note that frontal lobe dysfunction has also been found in obsessive-compulsive disorder by physiological (Malloy, 1987) and PET metabolic studies (Baxter *et al.*, 1987). To conclude, the findings reported here constitute a model of well-defined cerebral lesions which seem able to induce behavioural abnormalities mimicking some psychiatric symptoms. It may be

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INCLUSION BODY MYOSITIS

OBSERVATIONS IN 40 PATIENTS

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SUMMARY

Inclusion body myositis (IBM) was suspected on light microscopic grounds in 48 of 170 consecutive patients with inflammatory myopathies. One or more vacuoles containing membranous material, groups of atrophic fibres, and an autoaggressive endomysial inflammatory exudate occurred in 100, 96 and 92% of the muscle specimens. All three of these features were present in 88% of the specimens. Electron microscopy confirmed the presence of filamentous inclusions in 40 of 43 patients. The inclusions are typically near vacuoles and a minimum of three vacuolated fibres must be scrutinized to detect them with confidence. There is no electromyographic pattern that can reliably distinguish IBM from other inflammatory myopathies. The typical clinical features in the patients diagnosed by histological criteria as IBM were: insidious onset after age 50 yrs with painless, proximal lower extremity weakness; slow but relentless progression with selectively severe involvement of quadriceps, iliopsoas, tibialis anterior, biceps and triceps muscles; relatively early depression of the knee reflexes; and a normal or mildly elevated serum creatine kinase level. The male: female ratio was 3:1. Distal weakness occurred in about 50%, but only in 35% was it as great or greater than proximal weakness. Significant associated illnesses include other autoimmune disorders (15%), diabetes mellitus (20%), and diffuse peripheral neuropathy (18%). Prednisone treatment at dose levels frequently effective in polymyositis failed to prevent disease progression in those patients observed for 2 or more years. Our findings support the notion that IBM is a distinct entity in which a set of pathological features is associated with a constellation of clinical findings.

INTRODUCTION

It is currently believed that inclusion body myositis (IBM) can be distinguished from other inflammatory muscle diseases by a combination of clinical and histopathological features (Chou, 1986). The clinical features, summarized by Carpenter *et al.* (1978) from a review of 14 cases, 6 their own, consist of a relatively benign and protracted course, absence of features of a connective tissue disease, frequent involvement of distal muscles, male predominance, and resistance to corticosteroid therapy. The characteristic histopathological findings are nuclear and cytoplasmic filamentous inclusions and vacuoles rimmed by basophilic material in the muscle fibres. The inclusions, first described by Chou (1967) in a case of

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'chronic polymyositis', resemble myxovirus nucleocapsids on electron microscopy, but an origin from myofilaments has also been suggested (Yunis and Samaha, 1971). Although the above criteria for the recognition of IBM have been generally accepted (Ketelsen *et al.*, 1977; Danon *et al.*, 1982; Julien *et al.*, 1982; Mikol *et al.*, 1982; Eisen *et al.*, 1983; Lazaro *et al.*, 1986; Calabrese *et al.*, 1987; Ringel *et al.*, 1987), a number of problems have become apparent in defining the clinical and morphologic boundaries of the disease.

Based on a review of 24 previously published cases, Julien *et al.* (1982) emphasized the diversity of the clinical and electromyographic (EMG) findings. Further, these authors and Lane *et al.* (1985) observed responsiveness to corticosteroid therapy. With regard to the morphological findings, rimmed vacuoles in muscle fibres can also occur in some familial distal myopathies (Markesbery *et al.*, 1977; Nonaka *et al.*, 1981), denervated muscle (Fukuhara *et al.*, 1980), and oculopharyngeal dystrophy (Tomé and Fardeau, 1980). Finally, filamentous inclusions, with or without rimmed vacuoles and similar to those found in IBM, have been detected in some hereditary distal myopathies (Markesbery *et al.*, 1977; Fukuhara *et al.*, 1982; Martin *et al.*, 1982; Matsubara and Tanabe, 1982; Kuzuhara and Nakanishi, 1984; Nonaka *et al.*, 1985), as well as in giant cell tumours of bone (Welsh and Meyer, 1970). Thus neither the rimmed vacuoles nor the filamentous inclusions are specific for IBM.

The character of the inflammatory exudate in IBM was further evaluated by Arahata and Engel (1984, 1988*a*, *b*). The exudate was predominantly endomysial; perimysial inflammation was sparse or absent. The endomysial inflammatory cells were T cells and macrophages, present in a 2:1 ratio, many of the endomysial cells focally surrounded and invaded nonnecrotic muscle fibres, and the majority of the autoaggressive T cells were $CD8^+$ cytotoxic cells. However, the composition and autoaggressive character of the endomysial inflammatory exudate were similar to those observed in polymyositis. Further, some patients diagnosed as having IBM had no inflammatory cells in their muscle biopsy specimens (Ketelsen *et al.*, 1977; Carpenter *et al.*, 1978; Eisen *et al.*, 1983).

In addition to these observations, EMG (Eisen *et al.*, 1983) and nerve biopsy (Lacy *et al.*, 1982) studies have suggested a neurogenic disturbance in some cases of IBM. This notion has been further supported by the presence of both large and small polyphasic motor unit potentials (Carpenter *et al.*, 1978; Danon *et al.*, 1982; Julien *et al.*, 1982; Ringel *et al.*, 1987) and the frequent occurrence of groups of atrophic muscle fibres (Carpenter *et al.*, 1978).

From the above studies it is clear that none of the clinical, morphological or EMG features of IBM can be viewed as specific. Therefore, the validity of the diagnosis of IBM on morphological grounds alone, and even the notion that combined clinical and laboratory data provide a firm basis for the diagnosis may justifiably be questioned. To resolve this problem, we reviewed our experience with all patients seen over a period of three years in whom the diagnosis of IBM was initially suspected on light microscopic grounds. The following questions were asked. (1) Can light microscopic findings thought to be typical of IBM predict the electron microscopic (EM) detection of filamentous inclusions in muscle fibres? (2) Are the typical light and electron microscopic findings associated with clinical features thought to be typical of IBM? (3) Is there a characteristic EMG pattern? (4) Is there a concomitant neuropathy, and if so, what is its prevalence? (5) Can the criteria used for the diagnosis of IBM predict refractoriness to prednisone therapy?

MATERIAL AND METHODS

Forty-eight consecutive patients in whom 'probable' IBM was diagnosed by light microscopic criteria between March 1984 and March 1987 were studied.

Histopathological studies

The light microscopic histologic diagnosis of IBM was based on the presence of muscle fibres with single or multiple vacuoles rimmed with basophilic material plus one or more of the following features: (1) a predominantly endomysial mononuclear inflammatory exudate with sparse or absent inflammatory cells at perimysial sites; (2) invasion of nonnecrotic muscle fibres by endomysial mononuclear cells; (3) groups of atrophic muscle fibres; (4) small refractile eosinophilic inclusions in muscle fibres in haematoxylin and eosin-stained sections, but no cytoplasmic bodies in the same fibres in immediately adjacent trichrome-stained sections.

All biopsy specimens were from the triceps brachii or vastus lateralis muscles. Routine histochemical studies were performed on frozen sections (Engel, 1986). Sections stained with haematoxylin and eosin and with trichrome were analysed for the following: the frequencies (no. per area) of vacuolated fibres, nonnecrotic fibres invaded by mononuclear cells, and necrotic fibres; the frequency and distribution of inflammatory cells; and the frequency and size of atrophic fibre groups. The presence and frequency (no. per section) of eosinophilic cytoplasmic inclusions were also noted.

Muscle specimens were prepared for EM by standard methods (Engel, 1986). In each case, 20 semithin resin sections were examined by phase microscopy. Whenever possible, thin sections for EM were prepared from blocks containing vacuolated muscle fibres, and included one vacuolated and one or more nonvacuolated muscle fibres. From 3 to 20 blocks were thin sectioned for EM in each case. During the EM examination the frequency and location of the filamentous inclusions in the fibres were documented.

Electromyographic studies

Nerve conduction and needle EMG studies were performed according to standard techniques used in the Clinical Neurophysiology Laboratory of the Mayo Clinic (Daube, 1986). Fibrillation potentials (biphasic spikes or monophasic positive waves) in a given muscle were rated as 0 = absent, +1 = present in two areas, +2 = present in more than three areas, +3 = present in all areas examined, and +4 = dense discharges in all areas examined. The fibrillation index for a given muscle in the patient population was defined as the mean rating for that muscle × 10.

Motor unit potentials (MUPs) were evaluated according to their duration (normal, short and long) and configuration (normal or polyphasic). The amplitude of the MUPs was also assessed, but because this parameter closely followed the duration, only the duration was used in the final analysis. Parameters were graded subjectively by visual inspection on a scale from 0 (normal) to 4 (90–100% of the units outside the range of normal).

Clinical data

The medical records of patients in whom the diagnosis of 'probable' IBM was made on histological grounds were reviewed. Each patient's evaluation included a detailed history and neurological examination at the time of initial diagnosis and at least once during the follow-up. Significant aspects of the family history, presenting symptoms, and the duration of illness were determined from the history.

Muscle weakness was evaluated by the Mayo Clinic examination scale with 0 = normal to −4 = no movement at all. The severity of weakness of a given muscle in the patient population (severity index) was defined as the mean rating of that muscle ×(−10).

Functional capacity was rated on the following scale: 5 = minimal involvement; 4 = mild disability in independent daily functioning; 3 = requires assistance with daily activities; 2 = needs assistance with bodily functions/eating; 1 = bedridden or wheelchair bound. Although the patients in this series were all diagnosed between 1984 and 1987, some were followed for up to 20 yrs before the diagnosis was confirmed, allowing assessment of morbidity and mortality over an extended period of time.

The diagnosis of diffuse peripheral neuropathy was based on clinical and EMG criteria. The latter included slowing of multiple motor or sensory nerve conduction velocities and low sensory nerve action potential amplitudes not attributable to mononeuropathies. Values were compared with age-matched normals for our laboratory.

The erythrocyte sedimentation rate (ESR) (Westergren), serum creatine kinase (CK), and routine studies of blood and urine were obtained in all patients. Tests for rheumatoid factor, antinuclear antibody and serum paraprotein bands were obtained in some patients.

RESULTS

Light microscope observations

Among those patients who had muscle biopsies at the Mayo Clinic between March 1984 and March 1987, 170 had an inflammatory myopathy on histological grounds. In 48, or 28%, IBM was suspected on light microscopic grounds. Table 1 lists the pathological diagnoses in these patients.

Table 2 lists the incidence of the major pathological abnormalities and their quantitative assessment in the 48 muscle specimens. One or more fibres with rimmed vacuoles per low-power field (fig. 1A, B), groups of atrophic fibres

TABLE 1. PATHOLOGICAL DIAGNOSES IN 170 CONSECUTIVE INFLAMMATORY MYOPATHIES

	No.	%
Polymyositis	53	31.2
Inclusion body myositis	48	28.2
Dermatomyositis	31	18.2
Perivascular inflammation	14	8.3
Mixed connective tissue diseases	8	4.7
Eosinophilic fasciitis	5	2.9
Necrotizing vasculitis	4	2.3
Scleroderma with myositis	4	2.3
Granulomatous myopathy	2	1.2
Focal myositis	1	0.6

(fig. 1A, D), and endomysial inflammation (fig. 1A, C, D) occurred in 100, 92 and 96%, respectively. Further, 88% of the specimens displayed all three of these abnormalities. Refractile eosinophilic cytoplasmic inclusions were detected in 58% of the specimens (fig. 1D). The inclusions were sparse and seldom were more than 3 detected in a given section. Only 46% of the specimens displayed the combination of eosinophilic inclusions, rimmed vacuoles, endomysial inflammation, and atrophic fibre groups.

TABLE 2. LIGHT MICROSCOPIC ABNORMALITIES IN 48 MUSCLE SPECIMENS IN WHICH INCLUSION BODY MYOSITIS WAS DIAGNOSED

	Percentage of specimens	*Rating*	
		Mean	*Range*
Fibres with rimmed vacuoles	100	2.50	0.7–9[a]
Nonnecrotic fibres invaded by mononuclear cells	89.6	2.80	0–8[a]
Necrotic fibres	79.2	0.51	0–2[a]
Group of atrophic fibres	91.7	2.11	0–4[b]
Eosinophilic inclusions	58.3		
Inflammation			
Endomysial sites	95.8	1.8	0–4[c]
Perivascular sites	87.5	1.3	0–3[c]
Perimysial sites	37.5	0.3	0–1[c]

[a] Number/low-power field. In each case, 6 or more randomly selected 1.59 mm^2 fields were examined at a magnification of × 156 and the results were averaged. Table shows overall mean and range of individual means in 48 cases. [b] In each case, groups of atrophic fibres were scored in 6 or more randomly selected 1.56 mm^2 fields and the results were averaged. Table shows overall mean and range of individual means in 48 cases. In a given field the groups were scored as follows: $+1 = 3\text{–}5$ fibres per group, 1–2 groups; $+2 = 6\text{–}10$ fibres per group, or 3–4 smaller groups; $+3 = 11\text{–}20$ fibres per group, or 5–6 smaller groups; $+4 = > 20$ fibres per group or > 6 groups. [c] In each case, mononuclear cells were counted in 6 or more randomly selected 1.59 mm^2 fields; the counts were then averaged and scored as follows: $+1 = 3\text{–}10$ cells; $+2 = 11\text{–}25$ cells; $+3 = 26\text{–}50$ cells; $+4 = > 50$ cells. Table shows overall mean and range of individual means in 48 cases.

The inflammatory cells were most abundant at endomysial and least abundant at perimysial sites. Nonnecrotic fibres invaded by autoaggressive mononuclear cells (fig. 1C) and necrotic fibres were present in 92% and 79% of the specimens, but per unit area the invaded fibres were 2.6 times more frequent than the necrotic fibres.

All specimens with small groups of atrophic fibres also showed fibre splitting. Grouping of the histochemical fibre types (with more than 15 fibres of a given type adjacent to each other) was present in 3 patients: a diabetic with a peripheral neuropathy, a patient with EMG evidence for a peripheral neuropathy, and an octogenerian.

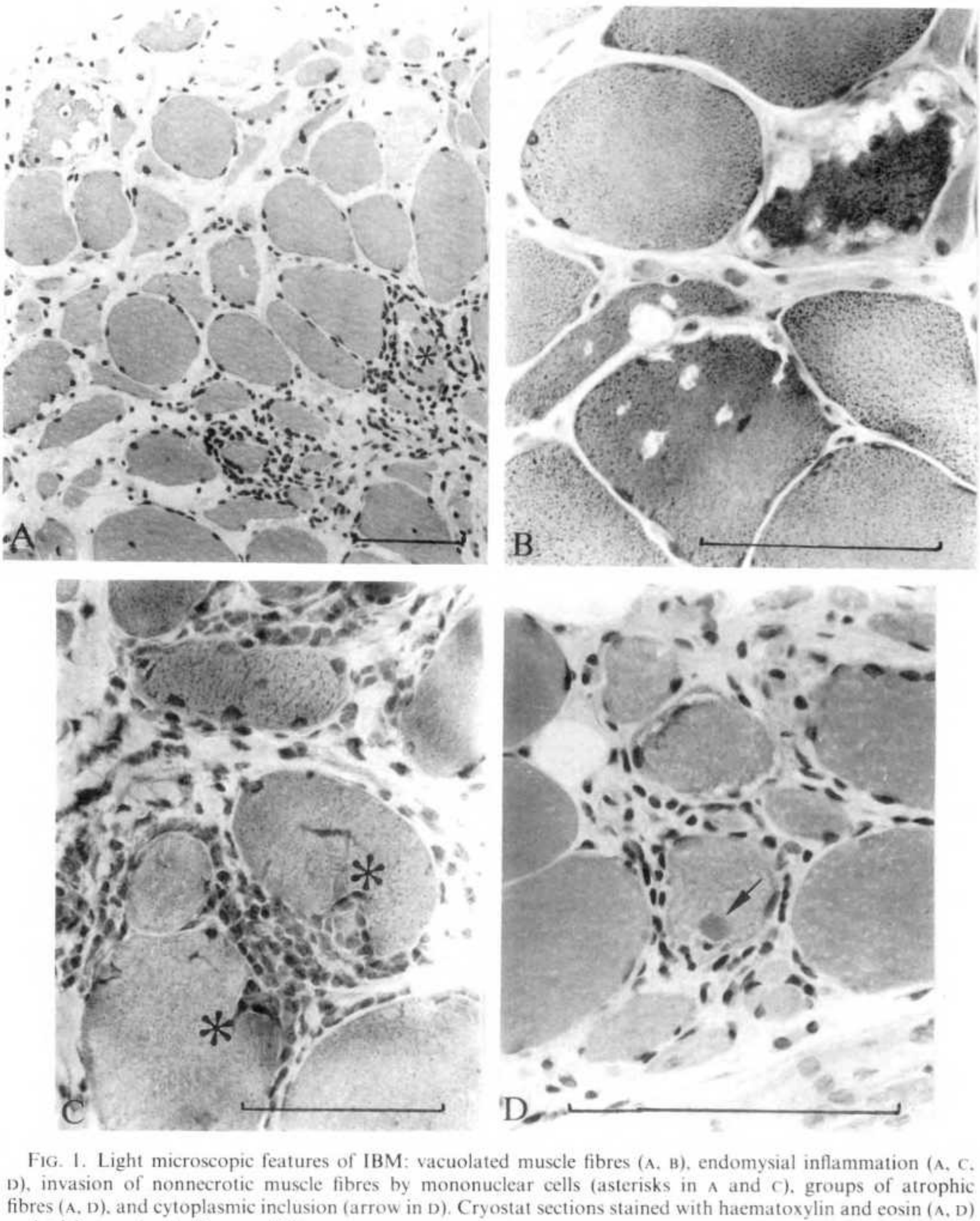

FIG. 1. Light microscopic features of IBM: vacuolated muscle fibres (A, B), endomysial inflammation (A, C, D), invasion of nonnecrotic muscle fibres by mononuclear cells (asterisks in A and C), groups of atrophic fibres (A, D), and cytoplasmic inclusion (arrow in D). Cryostat sections stained with haematoxylin and eosin (A, D) and trichrome (B, C). Bars = 100 μm.

Electron microscope observations

Material was available for EM from 43 of the 48 patients. The filamentous inclusions associated with IBM were observed in 40 (93%) (fig. 2). In 39 patients the inclusions were positioned near vacuoles (fig. 2A). Of the 115 vacuolated

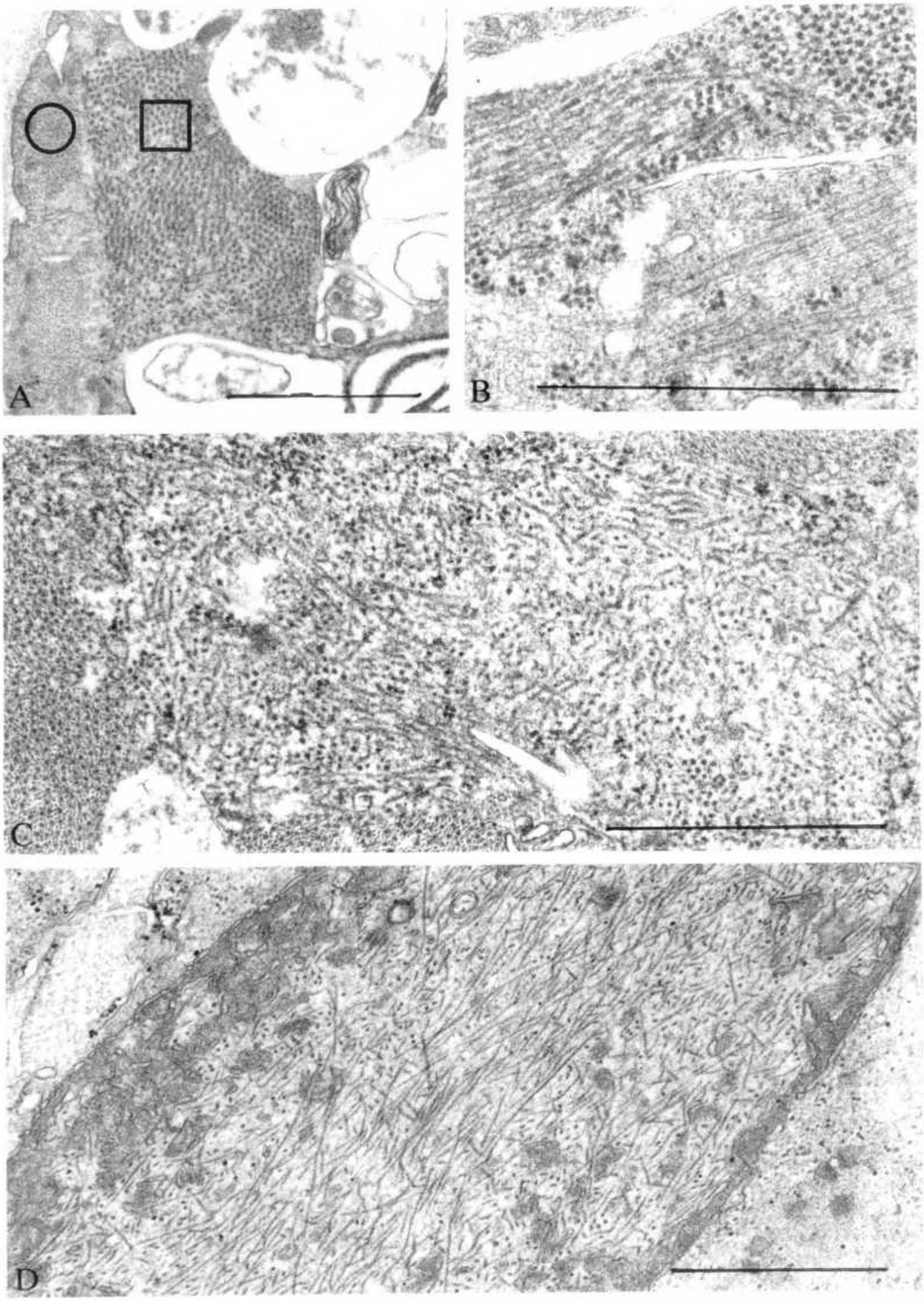

FIG. 2. Filamentous inclusions in IBM demonstrated by electron microscopy. The inclusions abut on a vacuole (A), are partially (B) or completely (C) surrounded by myofibrils, or are intranuclear (D). In A, region in circle contains a transversely sectioned double array of thick and thin myofilaments, and region within square contains transversely sectioned filaments of a cytoplasmic inclusion. The filaments in the cytoplasmic inclusion have larger diameters than the thick myofilaments. The filaments in the nuclear inclusion (D) are smaller in diameter than the cytoplasmic inclusions (A, B, C). Bars = 1 μm.

muscle fibres that were examined by EM, 39 fibres, or about 1 in 3, displayed an inclusion in the plane of sectioning. Intranuclear inclusions were encountered in 13 patients (fig. 2D). In 3 patients some inclusions were surrounded by, or abutted on myofibrils (fig. 2B, C). As noted in previous studies (reviewed by Mikol, 1986), the filaments were straight or curved gently and sometimes formed an interlacing meshwork (fig. 2C). The diameters of the cytoplasmic and intranuclear filaments were 17–21 nm and 10–14 nm, respectively. In 3 patients, EM failed to show inclusions. Two of these patients had no vacuolated fibres in resin sections, and the third had abnormally large and abundant mitochondria in many muscle fibres.

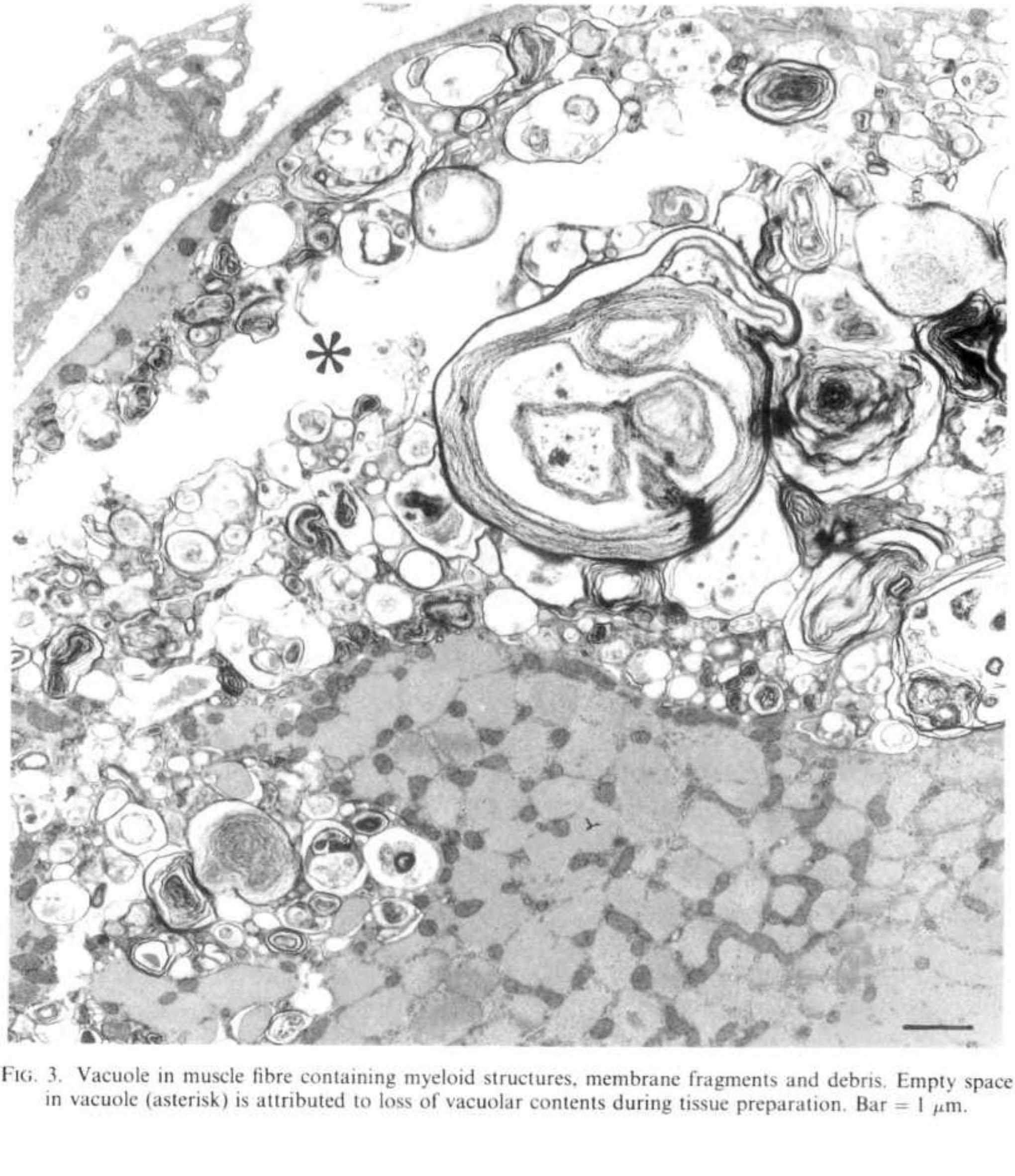

FIG. 3. Vacuole in muscle fibre containing myeloid structures, membrane fragments and debris. Empty space in vacuole (asterisk) is attributed to loss of vacuolar contents during tissue preparation. Bar = 1 μm.

The vacuoles were completely or partially filled with cytoplasmic degradation products consisting of myeloid structures, membrane fragments, and debris (figs 2A, 3). Although some of the intravacuolar structures were membrane-bound (fig. 2B), the vacuoles were never surrounded by a continuous membrane (fig. 3).

Clinical features

The data shown here pertain to the 40 patients in whom the diagnosis was confirmed by EM. However, the other 8 patients did not differ clinically or electrophysiologically from the rest.

There were 29 males and 11 females. The mean age at the onset of symptoms was 56.1 yrs (range 28–73 yrs). Only 7 patients were younger than 50 yrs and the age distribution was unimodal. The average duration from onset of symptoms to diagnosis was 6.3 yrs (range 0.5–19 yrs). None of the patients gave a history of a similar illness in the family. No particular occupational predisposition was recognized.

TABLE 3. SYMPTOMS IN 40 CASES OF INCLUSION BODY MYOSITIS*

Symptom	*No. at onset*	*No. at diagnosis*
Weakness	40	40
Dysphagia	4	16
Fatigue	0	4
Muscle aching/pain	0	8
Numbness/paraesthesiae	0	6

* Diagnosis confirmed by electron microscopy.

Table 3 lists the symptoms at the onset and at the time of diagnosis in the 40 patients. In 30 the initial weakness involved only the lower limbs, in 4 only the upper limbs, and in 6 both the upper and lower limbs. Lower limb weakness was initially proximal in 29, distal in 3, and diffuse in 4. Upper limb weakness was initially proximal in 4, distal in 4, and diffuse in 2.

The most severely affected muscles were biceps, triceps, iliopsoas, quadriceps and tibialis anterior (severity index > 14). Deltoid, pectoralis major, forearm and intrinsic hand muscles were less involved (severity index 9–12). Still less affected were the neck flexor, hip adductor, gluteal, hamstring, calf and toe flexor muscles (severity index 5–9). Facial muscles were slightly affected in a few patients. External ocular muscles were never involved. Upper limb weakness was greater proximally than distally in 18 patients, greater distally than proximally in 5, and diffuse in 17. For the lower limbs the corresponding figures were 28, 6 and 6. When all limbs were considered together, some distal weakness was detected in 50% of the patients, but only in 35% was it as great or greater than the proximal weakness. Muscle atrophy was proportional to weakness; muscle hypertrophy was never observed.

The tendon reflexes were commonly affected. Thus in the upper limbs they were reduced in 13 patients and absent in 6; in the lower limbs they were reduced in 15 and absent in 13. The knee reflex was invariably reduced or absent within 5 yrs of the diagnosis, and was absent 10 yrs after the diagnosis in all but 1 patient. In most patients, the depressed reflexes correlated with the degree weakness at the specific site of testing. However, 7 patients with EMG evidence for a diffuse peripheral neuropathy also had diffuse hyporeflexia. None of the patients exhibited extensor plantar responses, but brisk reflexes in 2 patients initially suggested a clinical diagnosis of motor neuron disease. Sensation was abnormal in 3 patients with EMG evidence for a peripheral neuropathy.

TABLE 4. FINDINGS ON BARIUM SWALLOW IN 12 PATIENTS WITH DYSPHAGIA*

	No. of patients
Decreased or absent peristalsis	5
Prominent cricopharyngeal muscle	5
Proximal stricture	3
Zenker's diverticulum	2
Distal diverticulum	1
No abnormality	2

* Findings not mutually exclusive.

Of 16 patients who had dysphagia at the time of diagnosis, 12 had a barium swallow examination (Table 4). In most of these patients the dysphagia could be related to upper oesophageal dysfunction.

Associated diseases

Table 5 lists other diseases diagnosed in the 40 patients with IBM. Cardiovascular abnormalities were the commonest, and are detailed in Table 6.

Of the 7 patients with a mild diffuse peripheral neuropathy, 3 had insulin-dependent diabetes mellitus; 4 had no predisposing condition. Eight patients had diabetes mellitus, but only 3 had an associated neuropathy. Four other patients, all receiving corticosteroids, had mild fasting hyperglycaemia. The mononeuropathies were caused by compression of the median nerve at the wrist in 4, and of the ulnar nerve at the elbow in 1.

Although 6 patients had had a malignancy, in only 2 was there a temporal association with IBM: in a 69-yr-old woman carcinoma of the breast and in a 67-yr-old woman carcinoma of the uterus were diagnosed shortly after the diagnosis of IBM. In the remaining 4 patients melanoma of the skin, carcinoma of the prostate and carcinoma of the breast presented 5, 10 and 19 yrs before, and squamous cell carcinoma of the lip 2 yrs after the onset of IBM symptoms.

Autoimmune diseases occurred in 6 patients. Of these a man with dermatomyositis was of special interest. Muscle weakness and a skin rash appeared at the age of 28 yrs. Two separate muscle biopsies shortly after the onset demonstrated an

TABLE 5. ASSOCIATED DISEASES IN 40 CASES OF INCLUSION BODY MYOSITIS[a]

	No. of patients
Cardiovascular diseases	22[b]
Peripheral neuropathy	11
Mild, diffuse	7
Mononeuropathy	5
Diabetes	8
Malignancy	6[c]
Asymptomatic paraproteinaemia	1
Paraproteinaemia with pancytopenia	1
Autoimmune disease	6
Idiopathic interstitial pneumonitis	2
Psoriasis	2
Dermatomyositis	1
Systemic lupus erythematosus	1

[a] Diagnosis confirmed by electron microscopy. [b] Abnormalities listed in Table 6. [c] In only 2 cases was there a close temporal association of malignancy with IBM.

TABLE 6. CARDIOVASCULAR ABNORMALITIES IN 40 PATIENTS WITH INCLUSION BODY MYOSITIS*

	No. of patients
Hypertension	18
Myocardial infarction	5
ECG changes compatible with ischaemia	8
Conduction defects	3
Rhythm disturbances	9
Valvular disease	4
Hypertrophic cardiomyopathy	1
Signs of cardiac failure	2
Axis deviation	6

* Diagnosis confirmed by electron microscopy. At least one cardiovascular abnormality was present in 22 patients; multiple abnormalities occurred in some patients.

inflammatory myopathy. The skin changes, which were typical of dermatomyositis, responded to corticosteroid therapy, but the muscle weakness never abated. A third muscle biopsy 19 yrs after the onset revealed the typical features of IBM.

Other diseases, not listed in Table 5, were chronic obstructive airways disease, interstitial cystitis, duodenal ulcer and rectal polyps, found in 1 patient each.

Electromyographic studies

Motor and sensory nerve conduction velocities and sensory nerve action potential amplitudes were normal in most patients. Abnormal values were found only in the 11 patients in whom a polyneuropathy or mononeuropathy was diagnosed by EMG and clinical criteria. F wave latencies were normal in all patients suggesting normal proximal nerve conduction. Distal latencies were prolonged only in the 4 patients with median neuropathies at the wrist.

During needle electrode studies, 5 to 12 muscles were examined in all patients. Distal and proximal muscles were tested in both the upper and lower limbs. The results are summarized in Table 7. Abnormal spontaneous electrical activity was observed in all patients. The increased insertion activity showed no predilection for a specific muscle group. Decreased insertion activity was observed in the more severely affected muscles. The fibrillation index closely mirrored the distribution of weakness (data not shown). An exception was the gastrocnemius muscle in which fibrillation potentials were abundant, but strength was usually preserved.

TABLE 7. ELECTROMYOGRAPHIC ABNORMALITIES IN 40 PATIENTS WITH INCLUSION BODY MYOSITIS*

	% of abnormal muscles among all muscles tested in all patients	*% of patients with abnormality in at least one muscle*
Abnormal spontaneous activity		
Insertion activity		
Increased	65.0	100
Decreased	6.2	25
Fibrillation potentials	75.2	100
Complex repetitive discharges	5.0	30
Myotonic discharges	2.6	12.5
Fasciculation potentials	1.7	10
Motor unit potentials		
Short duration potentials	77.0	100
Long duration potentials	40.0	77.5
Short and long duration potentials in same muscle	26.0	75
Polyphasic potentials	61.0	97.5

* Diagnosis confirmed by electron microscopy.

An increased incidence of short duration motor unit potentials was observed in all patients; 31 also had an increased incidence of long duration potentials, and 30 had an increased incidence of both short and long duration (or mixed) potentials in at least one muscle tested. In all patients, most of the long duration potentials were also polyphasic. The short duration potentials were commonly observed in both proximal and distal muscles and appeared in a higher proportion of muscles than long duration potentials. In the lower limbs, long duration potentials were observed more frequently in distal than proximal muscles. Mixed potentials were encountered in about the same proportion of muscles as long duration potentials.

Since the presence of mixed motor unit potentials in a given muscle may be evidence for a concomitant neuropathy, and because this feature has been repeatedly described in IBM (*see* Introduction), we evaluated the specificity and

TABLE 8. ANCILLARY STUDIES IN PATIENTS WITH INCLUSION BODY MYOSITIS

Test	*No. tested*	*No. abnormal*	*Mean*	*Range*
Sedimentation rate, mm/h[a]	40	7	16.0	1–72
Creatine kinase, U/l[b]				
Males	29	23	199.7	53–605
Females	11	9	189.6	23–566
Glucose, mmol/l[c]	40	14	5.9	4.1–9.4
Rheumatoid factor[d]	26	1	—	—
Antinuclear antibody[e]	32	6	—	—

[a] Normal: males < 22, females < 29. [b] Normal: males < 99, females < 57. [c] Normal: < 5.6 mmol/l. [d] Abnormal if > 70 IU/ml. [e] Abnormal if titre > 1:160.

significance of the mixed potentials in two ways. First, we reviewed the final diagnoses in 55 consecutive patients in whom mixed potentials were detected in at least one muscle at the time of EMG. This revealed that mixed potentials can be associated with a variety of myopathies (inflammatory myopathies other than IBM, congenital myopathies, limb girdle dystrophy, nonspecific myopathy) or with neurogenic diseases. Secondly, we reviewed the EMG records of 42 consecutive patients in whom the histological and clinical diagnosis was polymyositis. Muscle specimens from these patients showed no rimmed vacuoles or eosinophilic inclusions that would have suggested IBM, or perifascicular atrophy commonly present in dermatomyositis. Twenty-three of the 42 polymyositis patients, as compared with 30 of 40 IBM patients, had mixed potentials in at least one muscle. By χ^2 comparison, the two proportions were not significantly different ($P > 0.05$). However, in both diseases, the proportion of patients with mixed potentials was significantly higher when the disease duration was greater than 2 yrs ($P < 0.05$ for polymyositis and < 0.02 for IBM).

Ancillary laboratory studies

These are listed in Table 8. The serum CK level was slightly or moderately increased in 80% of the patients. None of the patients had CK levels more than 10 times above the upper normal limit. The ESR was abnormal in only 18%. Of the 6 patients with a positive test for antinuclear antibody, 1 each had systemic lupus erythematosus, interstitial pneumonitis, and psoriasis, and 3 had no associated disease.

Therapy

Twenty-nine patients had had prednisone therapy consisting of at least 40 mg/day for 3 months. A few reported temporary arrest of disease progression; the serum CK decreased in 4; and 1 improved in muscle strength and serum CK level after 5 months. Twenty-five of the 29 patients were observed for 2 or more years. All 25 showed progression of weakness despite therapy. Other immunosuppressants were also tried, but not according to a protocol, or not for a sufficient length of time to permit evaluation of their efficacy.

Prognosis

Twenty-eight patients were followed for a mean period of 72 months. Table 9 depicts the slow relentless progression of the disease. The 6 patients observed for 15 yrs or longer had become severely incapacitated. One was bedridden after 10 yrs and died of respiratory and cardiac failure 12 yrs after the onset of the disease.

TABLE 9. PROGRESSION OF FUNCTIONAL DISABILITY IN 28 PATIENTS*

Time since onset of symptoms (yrs)	*No. of evaluations*	*Mean functional capacity*
1–4	21	4.2
5–9	19	4.2
10–14	8	3.4
15–19	5	3.2
20	1	3.0

* Fifty-four evaluations were obtained in 28 patients. Up to 4 evaluations at different time points were obtained in some patients.

DISCUSSION

Histopathological features

In the present study the light microscopic diagnosis of 'probable' IBM was made on the basis of muscle fibres harbouring rimmed vacuoles plus one or more associated features (*see* Materials and Methods). Using these criteria, a triad of (1) one or more rimmed vacuoles per low-power field, (2) one or more groups of atrophic fibres per low-power field, and (3) a predominantly endomysial and autoaggressive inflammatory exudate was observed in 88%; this triad plus eosinophilic cytoplasmic inclusions were present in only 46%. Further, 93% of the probable cases were 'confirmed' as IBM by demonstrating filamentous inclusions at EM.

On EM, filamentous inclusions were found adjacent to vacuoles in all but 1 confirmed case. Our data indicate that a minimum of 3 vacuolated fibres must be scrutinized to detect inclusions with confidence. Conversely, if fewer than 3 vacuolated fibres are available for EM examination, failure to detect inclusions does not fully exclude the diagnosis of IBM. Since 2 of our 3 EM-negative cases had no vacuolated fibres in resin sections, the true predictive value of the light microscopic criteria may be greater than 93%.

Before accepting the filamentous inclusions in an inflammatory myopathy as a criterion for the diagnosis of IBM, one may also ask how often identical inclusions occur in inflammatory muscle diseases when they are not suspected by light microscopy. The constant association of the inclusions with rimmed vacuoles in IBM in and of itself suggests that inclusions would be uncommon or absent in inflammatory myopathies without rimmed vacuoles. Further, in recent EM studies in this laboratory of 18 cases of dermatomyositis and 15 of polymyositis, in which multiple tissue blocks comprising numerous muscle fibres were scrutinized in each case, no filamentous inclusions were encountered.

Incidence and clinical features

In the present series 'probable' and 'EM-confirmed' IBM comprised 28% and 23.5%, respectively, of all inflammatory myopathies. This proportion is even higher than the 15-17% reported previously (Carpenter *et al.*, 1978; Danon *et al.*, 1982; Chou, 1986). However, the nature of referrals to large medical centres is likely to distort incidence estimates.

The typical clinical features of IBM in the present series were: (1) onset after the age of 50 yrs, (2) male preponderance, (3) an insidious onset of painless proximal lower extremity weakness, (4) slow progression with selectively severe involvement of quadriceps, iliopsoas, tibialis anterior, biceps and triceps muscles, (5) relatively early depression of the knee reflex, and (6) normal or mildly elevated serum CK level.

The late onset and male preponderance noted in the present series are consistent with observations made by Danon *et al.* (1982), Julien *et al.* (1982) and Ringel *et al.* (1987). A bimodal age distribution for IBM, with peaks in the second and sixth decades (Eisen *et al.*, 1983; Chou, 1986) could not be confirmed. A bimodal distribution could result, however, from including hereditary distal myopathies with rimmed vacuoles under the rubric of IBM (Fukuhara *et al.*, 1982). In contrast to IBM, in large series of polymyositis an earlier mean age of onset and female preponderance have been observed (Rose and Walton, 1966; DeVere and Bradley, 1975; Henriksson and Sandstedt, 1982). The insidious onset of IBM also differs from that of polymyositis in which symptoms usually evolve over weeks or months (Rose and Walton, 1966).

Weakness of distal muscles equal to or greater than that of proximal muscles has been reported in IBM (Jerusalem *et al.*, 1972; Carpenter *et al.*, 1978; Eisen *et al.*, 1983), but only the minority of our patients showed this pattern. The disease seldom presented with distal weakness. Although at the time of diagnosis some distal weakness was present in 48%, proximal weakness was present in 90%, and distal weakness was as great or greater than proximal weakness in only 35%. Further, some patients with polymyositis also present with distal weakness (Sundaram and Ashenhurst, 1981), or eventually develop severe distal muscle involvement (Marconi *et al.*, 1982).

Dysphagia, also noted in other studies (Danon *et al.*, 1982; Julien *et al.*, 1982; Chou, 1986; Ringel *et al.*, 1987), occurred in 40% of our patients. In 5, the dysphagia could be attributed to cricopharyngeal dysfunction. This has been described in other inflammatory myopathies (Dietz *et al.*, 1980; de Merieux *et* *al.*, 1983; Kagen *et al.*, 1985; Horowitz *et al.*, 1986), but not in IBM. Its recognition is important because it is amenable to surgical therapy.

Electromyographic features

The needle EMG findings were like those found in patients with other inflammatory myopathies in terms of the abnormal spontaneous electrical activity, short duration motor unit potentials, and increased incidence of polyphasic potentials (Daube, 1986). The combined presence of long and short duration motor unit potentials (so-called 'mixed' potentials) in single muscles were seen in 30 of 40 patients. This finding was of special interest as it has been repeatedly described in IBM (*see* Introduction), and could be interpreted as an associated neurogenic feature. However, mixed potentials are not specifically associated with a neurogenic disorder. This is well illustrated by the analysis of 55 consecutive patients who had mixed potentials on EMG examination, and by the comparison of the 40 consecutive cases of IBM with 42 consecutive cases of polymyositis (*see* Results). A frequent association of long duration polyphasic potentials with short duration potentials in inflammatory myopathies was recently also noted by Uncini *et al.* (1987). Our findings suggest that mixed potentials reflect disease chronicity rather than a neurogenic aetiology.

Associated diseases

The 55% incidence of cardiovascular signs and symptoms in our 40 patients with IBM is close to the 49% incidence in the 107 patients with polymyositis studied by Henriksson and Sandstedt (1982). Increased morbidity and mortality from cardiovascular diseases also has been noted in other studies of idiopathic inflammatory myopathies (DeVere and Bradley, 1975; Henderson *et al.*, 1980; Strongwater *et al.*, 1983; Raju *et al.*, 1984; Rechavia *et al.*, 1985). In some patients an inflammatory basis for the myocardial disease has been established (Haupt and Hutchins, 1982; Weiss *et al.*, 1982). It remains to be seen if such a basis also exists in IBM.

In our group of 40 patients, other autoimmune diseases were detected in 6, or 15% (Table 5). In 3 additional patients a positive antinuclear antibody test gave evidence of disturbed immune regulation. Other recent reports describe IBM occurring with systemic lupus erythematosus (Yood and Smith, 1985), Sjögren's syndrome (Gutmann *et al.*, 1985), and dermatomyositis (Lane *et al.*, 1985). Therefore, the absence of features of a connective tissue disease, emphasized in earlier studies (Carpenter *et al.*, 1978; Mikol, 1986), is not characteristic of IBM. The 15% incidence of autoimmune diseases in this series is identical with that noted in 107 patients with polymyositis by Henriksson and Sandstedt (1982).

Clear clinical and EMG evidence for a mild, diffuse peripheral neuropathy was found in 7 patients, but in 3 diabetes mellitus was the probable cause. These data do not indicate that a diffuse peripheral neuropathy is an essential or important feature of IBM.

Although motor nerve conduction velocities were normal in most patients, the groups of atrophic muscle fibres and the mixed motor unit potentials in some muscles of most patients could suggest a distal motor axonal neuropathy. Although this possibility cannot be entirely excluded, it is unlikely because (1) normal intramuscular nerves were observed in several muscle specimens in which a large proportion of the fibres was atrophic; (2) grouping of histochemical fibre types, indicating reinnervation, occurred in only 3 patients, 2 of whom had other evidence of a neuropathy; (3) muscle fibre atrophy can be myogenic as well as neurogenic; and (4) the mixed potentials lack specificity.

The 20% incidence of diabetes mellitus in our patients is higher than the 3–7% incidence in residents of similar age in Rochester, Minnesota (Palumbo *et al.*, 1976). The relevance of this finding to the pathogenesis of IBM remains unclear.

Our data fail to show a significant association of IBM with malignancy. Although malignancies were found in 6 patients, a close temporal association with IBM was noted only in 2. Chance association with malignancy is particularly likely in this age group, especially when diagnosis of one disease initiates a complete investigation. Retrospective studies of polymyositis and dermatomyositis indicate a 10–20% association with malignancy (reviewed by Mastaglia and Ojeda, 1985). However, in a recent study in which age-matched controls were used, Lakhanpal *et al.* (1986) failed to document this association even in polymyositis.

Therapy

Our data are consistent with previous observations that corticosteroid therapy is ineffective in IBM (Carpenter *et al.*, 1978; Donan *et al.*, 1982; Mikol, 1986; Calabrese *et al.*, 1987; Ringel *et al.*, 1987). The findings are clearly different from those in polymyositis where recent studies show a favourable response to immunotherapy in 50–69% of patients (Henriksson and Sandstedt, 1982; Baron and Small, 1985; Tymms and Webb, 1985). Nevertheless, it cannot confidently be assumed that IBM is always refractory to immunotherapy for the following reasons. (1) A transient response to therapy has been observed in some patients in this and other (Julien *et al.*, 1982; Lane *et al.*, 1985) reports. (2) The total number of patients with IBM who have received immunotherapy is still relatively small, and only a few of these have had a systematic and sustained trial of one or more immunotherapeutic agents at the maximum tolerated dose. (3) As the disease progresses slowly, a therapeutic effect that consists of an arrest of disease progression rather than a reversal of deficits could be easily overlooked. Controlled therapeutic trials may clarify these points, but it is clear that rational therapy of IBM awaits a better understanding of its aetiology. Withholding treatment because the majority of patients fail to respond will deny the chance of improvement to a small minority who might respond. Therefore, at the present time, it would seem reasonable to consider at least one therapeutic trial with an immunosuppressant medication at the maximal tolerated dose over a period of 12 months. However, the risks of such therapy in a population of elderly patients must be weighed carefully in each case.

Is IBM a disease entity?

The present study supports the notion that IBM is a distinct entity in which a set of pathological features is consistently associated with a constellation of clinical findings.

The essential pathological features required for diagnosis are: (1) at least one rimmed vacuole per low-power field; (2) at least one group of atrophic fibres per low-power field; (3) an endomysial and autoaggressive inflammatory exudate; and (4) EM demonstration of the typical filamentous inclusions.

The light microscopic detection of eosinophilic inclusions (distinct from cytoplasmic bodies) supports but is not an essential requirement for the pathological diagnosis. The presence of pathological criteria 1, 2 and 3 predicts the presence of filamentous inclusions in 93% of the muscle specimens if at least 3 vacuolated fibres are scrutinized by EM.

The characteristic clinical features are: (1) insidious onset and slow progression of painless muscle weakness; (2) serum CK normal or less than 10 times above the upper limit of normal; (3) refractoriness to prednisone treatment at dose levels frequently effective for polymyositis; (4) EMG findings consistent with inflammatory myopathy; and (5) no evidence for a hereditary muscle disease.

Additional clinical findings helpful in the diagnosis are a pattern of maximum weakness in triceps, biceps, iliopsoas, quadriceps and anterior tibial muscles, and a depressed or absent knee reflex 5 yrs after diagnosis. IBM is consistently differentiated from ordinary polymyositis by pathological criteria 1 and 4, and by clinical features 1 and 3.

Finally, it is relevant to mention that Chou (1986) has found that the inclusions in IBM bound antibodies raised against mumps virus antigens. If confirmed, this observation would provide additional evidence for the existence of IBM as a nosological entity. However, Rammohan *et al.* (1988) and Nishino *et al.* (1989) were unable to demonstrate specific binding of antimumps antibodies in IBM. Thus the basic aetiology of IBM, like that of ordinary polymyositis, remains undefined.

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THE DISTRIBUTION OF MUSCULAR WEAKNESS IN UPPER MOTOR NEURON LESIONS AFFECTING THE ARM

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SUMMARY

The strength of 12 muscle groups of the arm was measured to determine the distribution of upper motor neuron weakness in man. Three groups of subjects were studied: 14 intact volunteers (both sides recorded), 10 patients with unilateral arm paresis (both sides recorded) and 6 patients with severe paralysis of the arm (the 'intact' arm only measured). On the side contralateral to the causative lesion the pattern of weakness was not the same in all patients. Shoulder muscles were relatively spared while the wrist and finger flexors were relatively severely affected, the difference being statistically significant. In hemiparetic and hemiplegic patients the strength of muscles ipsilateral to the lesion was reduced compared with normal controls. These observations refine previous clinical descriptions of upper motor neuron weakness and have implications for its pathophysiology.

INTRODUCTION

A lesion of the motor cortex or its descending projections, causing weakness associated with increased muscle tone and tendon reflexes, is described as an 'upper motor neuron' deficit. Much current knowledge of the distribution of the weakness is the result of careful observation of affected human subjects. The presence of selective weakness of particular muscle groups is important in understanding the resultant motor deficit. Furthermore, it may reveal the functional role of corticofugal pathways, in particular, the corticospinal system which reaches its greatest development in man (e.g., Phillips and Porter, 1977; Nathan and Smith, 1982).

Profound hemiplegia does not cause paralysis of all the muscles on one side of the body. Usually there is sparing of the muscles of the upper face, mastication, those of the trunk and respiration (Hughlings Jackson, 1865; Bastian, 1886; Gowers, 1893; Willoughby and Anderson, 1984). Broadbent observed that muscles

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always activated bilaterally were spared (Broadbent's 'law', Broadbent, 1866). The basis of this phenomenon was subsequently assumed to be bilateral representation of these muscle groups within the motor cortex (Gowers, 1893). Less severe lesions and recovery from complete paralysis have been reported to result in weakness with a characteristic distribution. Gowers (1893) summarized this as more marked weakness of distal rather than proximal muscles for both the arm and leg. Wernicke (1889) and Mann (1895) described the distribution of weakness between antagonistic muscle pairs acting at a single joint—in general, extensors of the arm and flexors of the leg appeared more weakened than their antagonists. Consistent with their description, extensors recover after flexors following paralysis of the upper limb but, paradoxically, flexors also recover first in the leg (Twitchell, 1951; *see also* Bard and Hirschberg, 1965). Walshe (1963) described a sequence of involvement of muscles with slowly progressive lesions. In the arm, most severely affected were isolated movements of the fingers and skilled movement of the hand, followed by extension of the wrist and fingers, extension of the elbow, and clenching of the fist. Elevation and adduction of the shoulder were least affected.

In a previous study, the distribution of weakness was specifically assessed for the flexors and extensors of the elbow in hemiparetic patients (Colebatch *et al.*, 1986). Unexpectedly, the elbow flexors rather than the extensors were relatively more weakened in the group of hemiparetic subjects. The present study extends these observations to include twelve muscle groups of the arm, thereby allowing comparison of their relative weakness in upper motor neuron lesions. In addition, we have attempted to find evidence to support the presence of an ipsilateral deficit by measuring the strength of the same muscles on the clinically intact side of patients with severe unilateral paralysis.

METHODS

The maximal voluntary strength of a variety of muscles of both upper limbs was measured. Observations were made on healthy volunteers and on a group of patients with unilateral arm weakness due to upper motor neuron lesions. The first group consisted of 14 subjects, 7 males and 7 females (mean age 47.0 yrs) without any history of neurological illness. Fourteen patients (9 males and 5 females, mean age 50.1 yrs), were also studied; 9 of the 14 had left-sided weakness, the remainder right-sided. They were selected from inpatients and outpatients attending the hospital during the course of the study. Patients with a history of an earlier stroke were not included. We also tried to avoid those who might have had other 'subclinical' lesions: preference was given to younger patients and those with lesions not due to atherosclerotic cerebrovascular disease. All had clinical features of upper motor neuron weakness (increased tendon reflexes in all, increased tone in 12 and a Babinski sign in 10; *see* Appendix). Thirteen were recovering from acute weakness and 12 were undergoing, or had completed active rehabilitation. For inclusion in the study the weakness had to be unilateral, both subjectively and to conventional clinical examination. During a preliminary neurological examination the selected patients appeared able to exert maximal effort. All were capable of activation of individual muscle groups on command. Spasticity was never severe. Sensory loss was variable but rarely marked. Patients with detectable strength at two or fewer joints in the upper limbs were considered 'plegic' and those with detectable strength at more than two joints as 'paretic'. Two patients, who recovered considerably, were studied when initially 'plegic' and later when 'paretic'.

Muscle strength was measured with specially designed myometers for the following muscle groups: abductors and adductors of the shoulder; extensors and flexors of the elbow, wrist, fingers and thumb; and abductors of the index finger. These results were calculated as torque about the joint. The strength of hand grip was measured with a dynamometer and expressed in Newtons. At the elbow the technique allowed direct measurement of torque and was the same as that described by Colebatch *et al.* (1986). For the other joints the measurements were made as force at the point of contact between the limb and the myometer and then converted to torque using the measured distance between the contact point and the axis of the joint under study. The degree of external restraint varied for the different muscle groups (fig. 1) and was greatest for the flexors and extensors

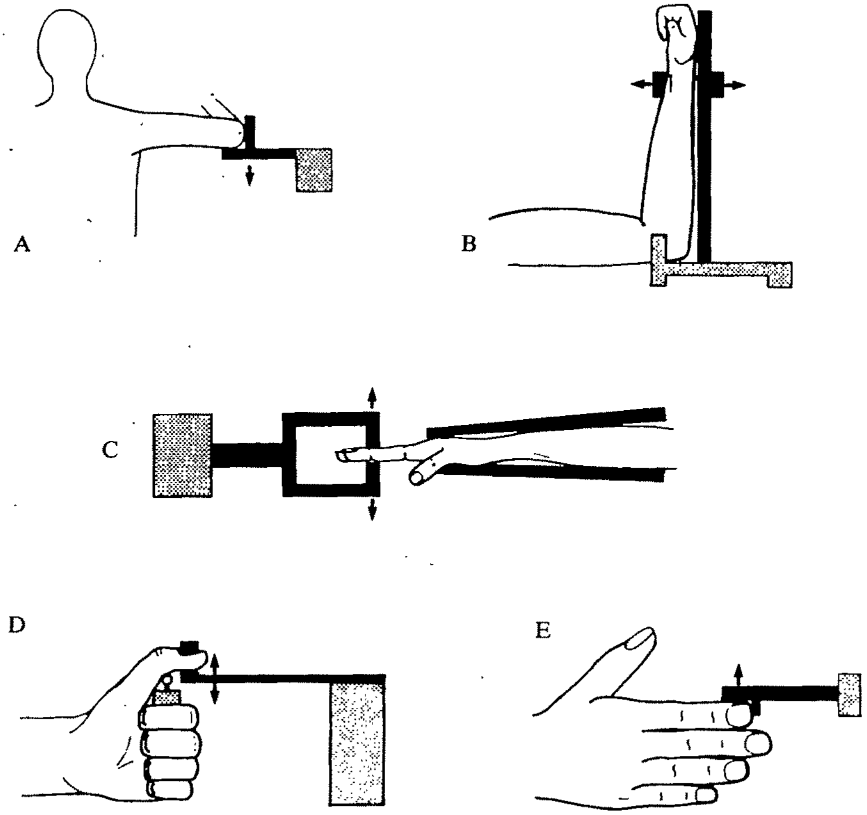

FIG. 1. Diagrammatic representation of the experimental methods used to measure strength of muscle groups in the upper limb. Steel bars with strain gauges bonded to their bases were used to measure force. At the shoulder (A), the subject sat with the arm abducted to 90° and either pushed down on the bar (for adduction, illustrated) or lifted up against it (abduction). At the elbow (B), the forearm was held to a myometer which was fixed coaxial with the joint, allowing direct measurement of both flexion and extension torque. Flexion and extension of the fingers were assessed with the fingers extended and held distal to the proximal interphalangeal joints between the two adjustable arms of the myometer (C). The forearm was immobilized between two steel supports. Wrist flexion and extension were measured in the same apparatus as (C) but with the forearm advanced to free the wrist joint and the distal clamp applied to the palm. Thumb flexion and extension were performed with the fingers gripping a support and the tip of the thumb clamped to the myometer (D). For abduction of the index finger (E) the finger abutted a thin length of steel and the palm was immobilized by one of the experimenters. Surface markings were used to calculate lever distances.

of the wrist and fingers and least for the muscles acting at the shoulder and for abduction of the index finger. One experimenter observed the subjects during each maximal effort and disqualified any contraction (without measurement) in which excessive use was made of remote synergistic muscles. An oscilloscope, visible to the subjects, displayed the force generated during each contraction (time base: 0.5 s/division). Loud verbal encouragement was provided for all contractions.

Different techniques and precautions were used for each of the muscle groups studied (*see* fig. 1). For the shoulder, the patient was seated and the arm abducted to 90°. The forearm rested against a stop to prevent it slipping along the myometer. The contraction was disallowed if the subject used the trunk muscles to flex the body towards the myometer. Shoulder abduction was measured with the arm beneath the bar and with the subject attempting to lift against it. Again the forearm rested against a stop (not shown in fig. 1). The weight of the arm was added to the force measured. The contractions were disallowed if significant elevation of the shoulder occurred. For measurements of elbow flexion and extension, the forearm was held against the myometer by an aluminium plate. The tip of the elbow was kept at the base of the instrument. Contractions were disallowed if the tip of the elbow moved from the base of the myometer. Measurements of the power at the wrist and fingers were made with a single myometer. Two sections of steel were pressed firmly against the forearm. An adjustable clamp at the end of the myometer could be applied either at the level of the palm (for wrist measurements) or at the level of the proximal interphalangeal joints (for finger measurements) with the forearm appropriately positioned to free or immobilize the wrist joint. Use of remote synergists was virtually impossible and it was only necessary to ensure that the fingertips did not touch the myometer during contractions. For measurements of thumb strength about the interphalangeal joint the subject grasped a cylindrical support and the distal phalanx of the thumb was clamped to the myometer. During thumb flexion, the subject's forearm remained in contact with the table surface. During extension, the metacarpophalangeal joint of the thumb and the wrist were stabilized by one examiner. For measurement of abduction of the index finger (the first dorsal interosseous muscle, FDI) the wrist and finger were initially straight with the tip of the index finger touching a stop. Radial deviation of the wrist and flexion of the finger were prevented during the contraction. The palm had to remain flat on the surface. Although the positions adopted for assessment of strength at most joints were similar to those used clinically, the present measurements are not necessarily directly analogous with clinical examination: here, isometric strength was measured whereas clinical testing usually consists of lengthening contractions (to 'overcome' the patient). Furthermore, we have attempted to measure the strength of the 12 muscle groups in isolation and to eliminate the need for postural fixation.

The stronger side was measured first for the patients and usually the right side for the healthy subjects. A minimum of 3 maximal contractions of 2–5 s duration was recorded. Further contractions were recorded if the last observation exceeded those before by more than 10%. The greatest value achieved was used in subsequent analysis. Because of the number of maximal contractions required to complete the full study (at least 72), observations were usually made in 2 separate sessions (24–72 h apart) to avoid fatigue.

RESULTS

Normal subjects

Fourteen subjects, 7 male and 7 female, were studied. None had a history of neurological abnormality. The strength of the 12 muscle groups was measured for both the right and left sides. The average values for the 12 muscles were not significantly different for the two sides, with 2 exceptions, both in females: elbow flexion and hand grip ($P < 0.05$, paired t test). As the difference between the means for these 2 muscle groups was less than 10% the values for the right and left sides

TABLE 1. NORMAL SUBJECTS: STRENGTH OF ARM MUSCLES*

	Shoulder		*Elbow*		*Wrist*		*Fingers*		*Thumb*		*Hand grip*	
	Ad	*Ab*	*Fl*	*Ex*	*Fl*	*Ex*	*Fl*	*Ex*	*Fl*	*Ex*	*(N)*	*FDI*
Females	36.2	26.7	39.3	19.3	7.05	5.59	4.96	1.79	0.83	0.26	286	1.13
(n = 7)	9.8	4.4	4.4	5.6	1.6	1.5	0.82	0.41	0.13	0.05	43	0.26
Males	68.9	45.8	70.8	33.6	12.8	10.0	7.90	2.71	1.40	0.37	410	1.91
(n = 7)	21.0	9.3	16.6	8.1	1.8	1.9	1.5	0.45	0.17	0.08	75	0.30

* Maximum strength (in Newton metres, Nm, except hand grip which is in Newtons, N) measured for 14 healthy volunteers. Mean values are given, with SDs below. Values for the right and left sides have been combined as they were rarely significantly different (*see* text). Elbow flexion is the strongest muscle group in both sexes and thumb extension the weakest. Ad = adduction, Ab = abduction, Fl = flexion, Ex = extension, FDI = first dorsal interosseous.

have been combined for all muscles (Table 1). Proximal muscle groups were stronger than distal muscles with the 4 strongest being the elbow flexors, shoulder adductors, shoulder abductors and elbow extensors (in descending order) for both sexes. The weakest muscles were the long flexor and extensor of the thumb and the first dorsal interosseous. Males were stronger than females and this difference was more pronounced for proximal muscles. Flexors were stronger than their antagonists. For the thumb and finger muscles the flexors were 3.5 and 2.8 times stronger than the extensors (corresponding to ratios for extensor-to-flexor strength of 29% and 35%, respectively).

Paretic subjects

Ten patients, 5 of each sex, were classified as 'paretic' (*see* Methods). The degree of their weakness was expressed by comparing the strength of each muscle group on their weak side with that on the stronger. This approach is analogous to that used in clinical examination but neglects potential ipsilateral effects. The strength of the muscle groups on the weak side varied from 2.5% to 99% of that on the spared side. Averaging the degree of weakness for the 10 subjects gave the following ranking for relative weakness (mean percentage residual strength is given in brackets): wrist flexion (32%), hand grip (34%), finger flexion (36%), thumb flexion (41%), thumb extension (42%), wrist extension (43%), elbow flexion (47%), finger extension (50%), abduction of the index (52%), elbow extension (53%), shoulder abduction (57%) and, least affected overall, shoulder adduction (67%). The distribution of weakness between the muscle groups did not conform to a common pattern in different patients; nor was any single muscle group always most severely affected (fig. 2). In specific cases the weakest muscle group was wrist flexion (2 subjects), wrist extension (2 subjects), hand grip (2 subjects) and abduction of the index finger (2 subjects). Abduction of the index finger showed the most variable degree of weakness. In 2 subjects it was the most severely affected muscle but in 3 others it was the least affected. Shoulder adduction was

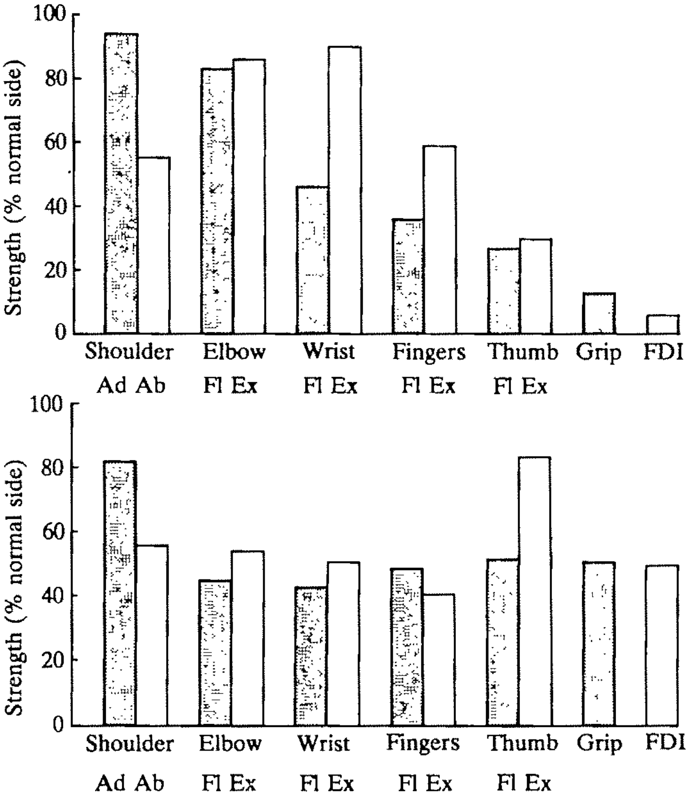

FIG. 2. Distribution of muscle weakness for 2 of the paretic subjects to reveal the variability encountered. The strength on the paretic side has been expressed as a percentage of the strength of the opposite (spared) side. The muscles are shown below the bars. For the subject shown in the *upper* half of the figure (*F2*, with an infarct of the corona radiata), distal muscles were more severely weakened than proximal ones. The subject shown in the *lower* half of the figure (*M5*, who had a distal occlusion of the basilar artery), had a similar degree of involvement of all muscle groups. Both subjects show that flexors were usually relatively weaker than extensors, although this difference was often small. Ad = adduction, Ab = abduction, Fl = flexion, Ex = extension.

TABLE 2. PARETIC PATIENTS: STRENGTH OF ARM MUSCLES (WEAKER SIDE)*

	Shoulder		*Elbow*		*Wrist*		*Fingers*		*Thumb*		*Hand grip*	
	Ad	*Ab*	*Fl*	*Ex*	*Fl*	*Ex*	*Fl*	*Ex*	*Fl*	*Ex*	(*N*)	*FDI*
Females (n = 5)	25.0	19.7	26.7	14.0	2.47	2.34	1.18	0.79	0.39	0.11	103	0.52
Males (n = 5)	20.0	12.7	13.1	9.46	2.80	1.65	2.18	0.67	0.40	0.17	78	0.78

* Paretic patients' residual strength (in Nm, except hand grip which is in N) of the 12 muscle groups on the clinically affected side. Mean values are given. In terms of absolute force, extensors are weaker than the corresponding flexors. *See also* figs 2 and 3. Abbreviations as in Table 1.

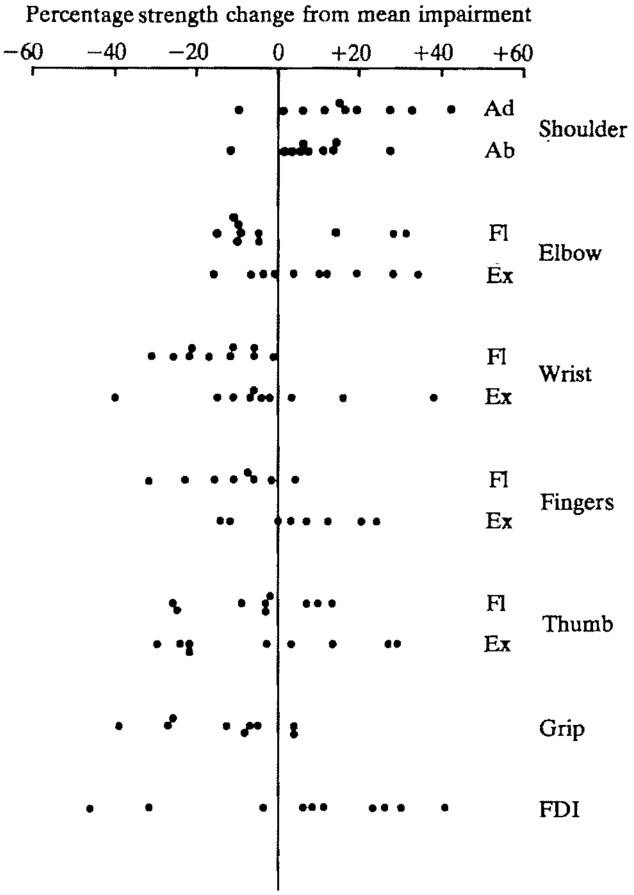

FIG. 3. Relative weakness of the 12 muscle groups for the hemiparetic subjects. The degree of weakness has been calculated by using the strength on the spared side as a reference. To facilitate comparison between the subjects, the weakness of each muscle group has been expressed relative to the overall weakness for each particular subject: thus for each subject the more severely affected muscles lie to the left of the line, the less severely to the right. Flexion at the wrist and fingers as well as hand grip were nearly always more severely affected than average. Shoulder adduction and abduction were usually relatively spared. The strength of abduction of the index finger (FDI) was variable.

least affected in 3 subjects and thumb extension in 2 subjects. An analysis of variance (two way, no replications) confirmed a significant muscle group difference. Shoulder adduction and abduction differed significantly from wrist flexion, grip and finger flexion (Duncan's multiple-range test). While flexors were on average more severely affected than extensors, these differences did not reach significance for any muscle group (fig. 3). The absolute strength for the paretic subjects is given in Table 2.

Plegic subjects

The use of the stronger side as a reference in the paretic patients assumed that there was no ipsilateral effect on voluntary strength due to cerebral or brainstem

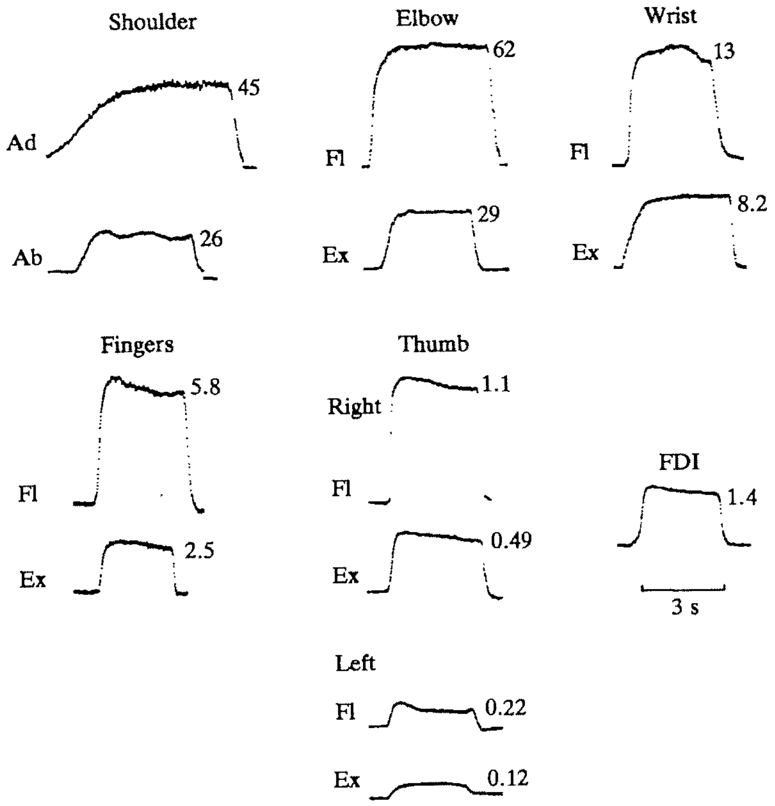

FIG. 4. Recordings from one 'plegic' subject (*M4*). Most of the figure shows the strength of the muscles on the (spared) right side. The figures near each contraction give the maximum torque achieved in Nm. Note the rapid achievement of maximum force and its constancy, typical of a well motivated subject. The lowest part of the figure shows the residual power of the left arm: flexion and extension of the thumb. Generally, as here, if a muscle group was relatively spared in the 'plegic' subjects, so was its antagonist.

lesions. This might not be the case (e.g., Brodal, 1973) so separate observations were made to detect evidence of ipsilateral weakness and its distribution. Six male subjects (mean age 50 yrs) were studied. All had severe unilateral weakness (mean duration 8 wks); 2 of them later recovered sufficiently to be remeasured and included in the paretic group (M2 and M5). Most of the muscles on their weak side were paralysed. When residual strength was present, it was nearly always measurable in both agonist and antagonist about a single joint (fig. 4). When the remaining strength of a muscle was greater than 2% (of that on the contralateral side), there was always measurable power in its antagonist.

The strength of the muscle groups on the apparently intact side was compared with the values obtained in normal subjects (Table 3). Most of the muscles on the spared side of the *plegic* subjects were weaker than those of the intact subjects ($P < 0.01$, sign test; mean reduction 12%). Shoulder adduction (62% of average value of normal controls) and wrist extension (63%) were the most severely affected; FDI (105%) and thumb extension (149%) the least. An analysis of variance confirmed the presence of significant differences between the muscle groups ($P < 0.01$). The power of the stronger (apparently normal) side of the paretics was also reduced when compared with control values ($P < 0.01$ by sign test), on average by 13%.

TABLE 3. PATIENTS: STRENGTH OF ARM MUSCLES (STRONGER SIDE)*

	Shoulder		*Elbow*		*Wrist*		*Fingers*		*Thumb*		*Hand grip*	
	Ad	*Ab*	*Fl*	*Ex*	*Fl*	*Ex*	*Fl*	*Ex*	*Fl*	*Ex*	(*N*)	*FDI*
'Paretic' patients												
Females (n = 5)	31.7	28.4	38.5	20.9	6.5	4.4	3.3	1.2	0.79	0.31	205	1.0
Males (n = 5)	47.5	34.0	53.4	26.3	11.5	6.8	7.0	2.3	1.1	0.43	325	1.8
'Plegic' patients												
Males	42.9	32.2	62.3	31.2	9.6	6.3	7.1	2.4	1.2	0.55	338	2.0
% normal	62	70	88	93	75	63	90	89	86	149	82	105

* Average strength of muscles on the 'spared' side for both 'paretic' and 'plegic' patients. The percentage of mean values for the normal subjects is shown for the 'plegic' patients. Abbreviations as in Table 1.

These findings support the presence of an ipsilateral effect on voluntary muscle strength following unilateral cerebral lesions. The degree of weakness for the paretic subjects was therefore recalculated using the average values from the control subjects instead of data from the paretic subjects' stronger side. However, this caused only minor changes in the ranking of the weakened muscle groups from that obtained using the stronger side as the reference. The 3 most severely affected muscle groups for the paretic subjects were still finger flexion, hand grip and wrist flexion. The 3 least affected muscles remained elbow extension, shoulder adduction and shoulder abduction. Statistically, these two rankings were highly correlated ($r = 0.85$, $P < 0.01$, Spearman rank correlation).

DISCUSSION

The 'upper motor neuron' syndrome is a common neurological abnormality and the typical weakness has been well described clinically. In contrast, there have been few studies attempting to quantify this weakness and the results have not always confirmed clinical impressions (Colebatch *et al.*, 1986). In this report we have measured the strength of 12 different muscle groups of the arm to determine the distribution of weakness both contralateral and ipsilateral to the responsible lesion. Quantitative myometry has been used previously in studies of peripheral neuromuscular disorders and with appropriate precautions has acceptable levels of reproducibility (Viitasalo *et al.*, 1980; Gandevia *et al.*, 1983; Wiles and Karni, 1983; van der Ploeg *et al.*, 1984).

A rigid hierarchy of involvement of different muscle groups was not observed for the patient's clinically affected side. There was partial sparing of the muscles of the shoulder and elbow, confirming previous clinical observations (*see* Introduction) and similar to the findings with experimental lesions in monkeys (e.g., Denny-Brown and Botterell, 1948; Fulton, 1943). In *relative* terms, extensors were not weaker than flexors and, in fact, the flexors of the wrist and finger were on average the most severely affected muscles. In terms of *absolute* force, extensors (of elbow, wrist, fingers and thumb) were, as in intact subjects, weaker than their corresponding flexors (Tables 1, 2). This may influence clinical impressions of the distribution of strength in hemiparesis, particularly the apparently selective involvement of extensors in the upper limb.

Early descriptions of hemiplegia (e.g., Hughlings Jackson, 1865; Bastian, 1886; Gowers, 1893) equated it with a lesion of the corticospinal tracts, the first recognized motor pathway (*see* Nathan and Smith, 1955). The terms 'pyramidal' and 'upper motor neuron' are still used interchangeably. However, subsequent evidence for the presence of other descending pathways as well as that from isolated lesions of the pyramidal tracts of man and monkey have shown this to be an oversimplification (e.g., Tower, 1940; Nathan and Smith, 1955; Lewis and Brindley, 1965; Brodal, 1969; Phillips and Porter, 1977; Ropper *et al.*, 1979; Kuypers, 1987). Thus the present findings do not necessarily indicate the relative 'potency' of corticospinal projections to the various muscle groups. Despite these reservations, it is of interest that corticospinal excitation (measured as EPSP size) is greatest for distal muscles (Phillips and Porter, 1964; M. Illert, R. N. Lemon, R. B. Muir and T. Yamaguchi, unpublished observations).

We found a reduction in average strength affecting most muscles on the clinically spared side of the plegic patients, thumb extension alone being an exception. (The latter finding requires confirmation, but may be the result of the intact subjects' failure to activate fully the muscle secondary to cutaneous inhibition; Gandevia and McCloskey, 1977.) Shoulder adduction was the most severely weakened muscle group on the apparently 'spared' side. This is unlikely simply to be the result of disuse as nearly all patients had completed or were undertaking active rehabilitation programs and thus would be expected to be using their 'intact' side more than usual. Ipsilateral deficits have been reported for more complex motor tasks (e.g., Brodal, 1973; Jones *et al.*, 1987) and Gowers (1893) stated that ipsilateral weakness was common following unilateral lesions ('the power of the hand is often reduced to not much more than one half of the normal', p. 77; *see also* Adams and vander Eecken, 1983). Our results confirm that the ipsilateral side is not physiologically 'normal'. Ipsilateral weakness would be expected to follow from unilateral lesions if each cerebral hemisphere has bilateral projections and these have been demonstrated in subhuman primates (e.g., Bucy and Fulton, 1933; Brinkman and Kuypers, 1973; Kuypers, 1987) and for cranial muscles in man

(Penfield and Jasper, 1954; Benecke *et al.*, 1988; Gandevia and Applegate, 1988). If all the arm muscles were in receipt of equal amounts of ipsilateral (bilateral) input, then it might be expected that the weakness on the 'spared' side of the paretic patients would parallel that of their affected side and that all muscles would be equally weakened on the 'spared' side of the plegic patients. The power of shoulder adduction in particular did not behave in this way. It was relatively little affected compared with other muscles on the 'paretic' side and relatively severely affected on the 'spared' side. This indicates that, if bilateral projections are responsible for the pattern seen, their influence must be relatively more pronounced for shoulder adduction than for other muscles such as the intrinsic muscles of the hand (fig. 5). Such a view is consistent with neuroanatomical data in nonhuman primates (Kuypers, 1987).

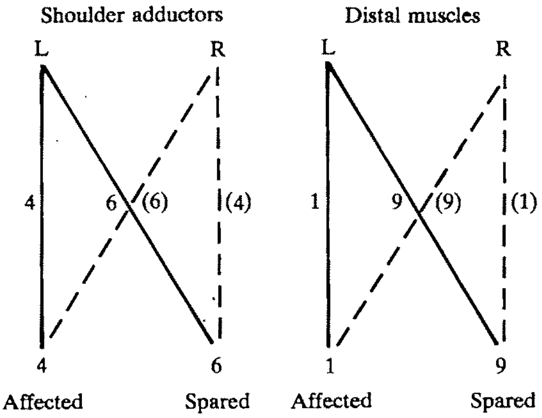

FIG. 5. Schematic representation, assuming the presence of bilateral projections, showing possible corticofugal output for shoulder adductors (*left*) and distal muscles (*right*). The strength of ipsilateral and contralateral projections is given by a number and the lesion affects the right hemisphere (dashed lines). Normal power is 10 for both muscle groups. On the weaker ('affected') side, distal muscles are more severely affected (1) and shoulder adductors relatively spared (4). By contrast, on the stronger ('spared') side, shoulder adduction is more impaired. This simplified scheme shows that the relative strength of the ipsilateral (bilateral) projection may determine the pattern of weakness that follows a unilateral cerebral lesion.

Detailed observations of human subjects with defined neurological lesions are the basis of much current neurological knowledge. Quantification of the deficits should allow refinement of classical clinical descriptions. The patients studied here had features typical of an upper motor neuron deficit, often with an acute onset. It may be that patients with progressive lesions will require separate consideration as there is evidence that the motor cortex may compensate partially for repeated small lesions (Glees and Cole, 1950; *see also* Rosen *et al.*, 1971). Further studies are required to understand both the mechanism of, and recovery from, this common syndrome.

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APPENDIX

CLINICAL DETAILS OF ALL PATIENTS STUDIED*

Case (age)	*Weak side*	*History*	*Duration weakness (wks)*	*Examination*	*Investigations*
M1 (71)	L	Hemiparesis following cardiac catheterization. PH hypertension	49	Hemianopia, mild facial weakness. Increased tone and reflexes with extensor plantar response. Reduced pin prick, joint position and vibration sense	CT scan: infarct R posterior parietal lobe, extending towards midline
M2 (58)	L	Onset of weakness over a few min with initial L hemianopia and dressing apraxia. PH hypertension	3, 10	Mild facial weakness. Increased tone and reflexes with extensor plantar response. Minor reduction in joint position sense L arm	CT scan: no focal lesion
M3 (60)	L	L sided weakness following clipping aneurysm at bifurcation of R internal carotid artery	6	R Horner's syndrome. Increased tone and reflexes. Sensory extinction in arm to light touch	CT scan: R internal capsule infarction

Appendix (*cont.*)

Case (age)	*Weak side*	*History*	*Duration weakness (wks)*	*Examination*	*Investigations*
M4 (43)	L	Developed L sided weakness following operative diathermy to turbinates	2, 4	R Horner's syndrome. Weak trapezius. Tone increased in leg but not in arm, with hyperreflexia and extensor plantar response. Reduced pin prick and joint position sense	R carotid angiography normal. CT scan: extensive oedema of R parietal lobe
M5 (35)	R	1 transient plegic episode with recovery, followed by recurrence of plegia with slow improvement	32	Mild facial weakness. Bilaterally brisk reflexes. Increased tone and extensor plantar response on R. Sensation intact	Angiography: distal basilar artery obstruction
M6 (28)	L	4 mo. history of occipital headaches and diplopia. Severe headache, diplopia and vertigo 1 day after manipulation of neck	5	Internuclear ophthalmoplegia on L gaze. Weakness affecting face, arm and leg with increased tone and reflexes and extensor plantar response. Mild reduction of joint position sense and 2-point discrimination for arm	CT scan: lesion R occipital lobe ?infarct. Angiogram/ distal basilar artery occlusion
M7 (65)	R	Acute onset of weakness one afternoon	9	Mild nominal dysphasia. Face, arm and leg weakened with hyperreflexia, increased tone and extensor plantar reponse. Sensation normal	CT scan: no abnormality
M8 (61)	R	Awoke with acute weakness and dysphasia during admission for correction of gastric stasis	11	Nominal dysphasia, R/L disorientation and dyscalculia. Face, arm and leg weakness, with increased tone, reflexes and extensor plantar response. Mildly reduced pin prick and joint position sense in arm	CT scan: large infarct in territory of L middle cerebral artery involving internal capsule
M9 (47)	R	Acute weakness and loss of consciousness during hypertensive crisis	15	Dysphasic but comprehension good. Weakness associated with increased tone and reflexes and extensor plantar response. All sensory modalities reduced on R	CT scan: intracerebral haemorrhage in region of L basal ganglia and internal capsule
F1 (20)	L	Hemiparesis following pyogenic meningitis	29	Deaf L ear. Predominantly distal weakness of arm. Hyperreflexia, increased tone and extensor plantar response. No sensory deficit in limbs	CT scan: R internal capsule infarct and periventricular white matter lesions
F2 (69)	L	Hemiparesis after mitral valve replacement, worse after repeat operation 5 months later	36 (54)	Distal arm weakness with increased tone and reflexes. Reduced vibration sense and 2-point discrimination	DS angiogram: normal. CT scan: infarct in R corona radiata

Appendix (*cont.*)

Case (age)	*Weak side*	*History*	*Duration weakness (wks)*	*Examination*	*Investigations*
F3 (47)	L	Dilated cardiomyopathy and chronic atrial fibrillation. Rapid onset of facial and limb weakness	15	Homonymous hemianopia with facial weakness. Increased tone, hyperreflexia and extensor plantar response. Reduced vibration and joint position sense and 2-point discrimination	CT scan: infarct in R middle cerebral artery territory
F4 (69)	L	Noted to be disorientated and losing her way. Debulking of high grade glioma and postoperative hemiparesis	3	Mild arm and leg weakness with hyperreflexia. No sensory deficit in arm	CT scan (preop.): Ring-enhancing parasaggital lesion in R parietal lobe
F5 (29)	R	Wear R arm since childhood with recent development of facial twitching	Yrs	Predominant arm weakness with hyperreflexia. Mild reduction in vibration and joint position sense	CT scan: calcified area in L parietal lobe. Angiography normal

* Cases M1, M3, M5 and F1–F5 were studied when 'paretic' and M6–M9 when 'plegic', while M2 and M4 were included in both categories (*see* Methods). Unless otherwise qualified, all deficits refer to the clinically weak side. PH = past history.

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THE TREATMENT OF SEVERE ACTION MYOCLONUS

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SUMMARY

Ten patients with severe disabling myoclonus were treated with clonazepam, sodium valproate, primidone and piracetam alone, or in different combinations. Electrophysiological assessment indicated a cortical origin for the myoclonus in every case. Considerable improvement of myoclonus was achieved with combinations of these drugs in all patients, but this was not possible with monotherapy. In one patient two drugs were necessary (clonazepam and piracetam); in the others more than two drugs were required. The combination of sodium valproate, clonazepam and primidone (3 patients), or piracetam, clonazepam and primidone (3 patients), or the four drugs together (3 patients) was necessary to provide substantial relief of myoclonus. Such polytherapy generally was tolerated well. The benefits of treatment continued for more than 1 year in all cases, although progressive underlying pathology often caused other increasing disability.

INTRODUCTION

Among the different types of muscle jerks, myoclonus occurring during voluntary movements (action myoclonus) is probably the most disabling. A number of static or slowly progressive conditions are now recognized in which severe multifocal and/or generalized action myoclonus is the main source of disability. Cerebral anoxia (Lance and Adams, 1963), head trauma, cerebellar degenerations and multiple system atrophies, mitochondrial encephalopathies and essential myoclonus are common causes (Fahn *et al.*, 1986; Lance, 1986).

In addition to action myoclonus, careful clinical examination of such patients often reveals the existence of myoclonic jerks provoked by somaesthetic stimulation of the limbs (reflex myoclonus). In a large proportion of these cases, detailed electrophysiological analysis demonstrates brief EMG discharges (10–50 ms), a EEG cortical discharge preceding the myoclonus by a short interval of some 20 ms for the upper limbs and 35–40 ms for the lower limbs, and an increase in amplitude of somatosensory evoked potentials, all indicating a cortical origin for the jerks (Hallett *et al.*, 1979; Obeso *et al.*, 1985*b*). However, action myoclonus

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may also have a subcortical origin, with the abnormal discharges arising from the brainstem, thalamus or basal ganglia (Halliday, 1975; Hallett, 1987).

Adequate control of severe action and reflex myoclonus is not always easy to achieve; 5-hydroxytryptophan (5-HTP) with carbidopa, clonazepam and sodium valproate, individually or in combination, are the drugs more commonly used (Pranzatelli and Snodgrass, 1985; Van Woert *et al.*, 1986). However, action and reflex myoclonus of cortical origin are often resistant to these individual treatments (Chadwick *et al.*, 1977; Kelly *et al.*, 1981). In this paper we describe how the combination of several antimyoclonic drugs may provide considerable relief of severe action myoclonus.

PATIENTS AND METHODS

Ten patients with severe action myoclonus secondary to anoxia (2 cases), head trauma (1 case), the Ramsay Hunt syndrome (defined as the clinical syndrome of progressive action myoclonus and ataxia, with infrequent grand mal seizures and little or no intellectual deterioration) in 4 cases, Lafora body disease (1 case), and 1 patient with focal right hand myoclonus of unknown aetiology, and another with multifocal myoclonus of unknown origin, have been selected from a large group of patients with myoclonus. The reason for this selection was that all had extremely severe action myoclonus, so that despite simple treatment they were bed-ridden when first seen.

The response to different drugs was assessed independently by at least 2 of the authors at the beginning, and on each occasion that a variation in the treatment was introduced, using a modification of the scale previously described by Chadwick *et al.* (1977). This scale, graded from 0 to 3, rates intensity, frequency and distribution of myoclonus, and the degree of functional impairment of normal daily life. Many of these patients had additional neurological deficits which impaired their motor function. The effect of treatment on both the myoclonus and the capacity to perform a series of motor tasks was evaluated as follows: *no response*, no change in myoclonus or motor ability; *slight response*, less than 30% reduction of myoclonus rating score, assistance still required for most motor tasks, walking possible with help; *moderate response*, 30-70% improvement in the myoclonus score, patients could walk, eat and drink, but were not completely independent; *dramatic response*, 70-100% control of the myoclonus, patients were able to perform all motor activity without help.

Electrophysiological investigations were undertaken in each patient to assess the source of the myoclonus. Cerebral somatosensory evoked potentials (SEPs) and electromyographic (EMG) recording of the muscle jerks evoked by digital nerve stimulation were simultaneously recorded. When possible, the technique of back-averaging the EEG activity preceding the muscle jerks was applied. Myoclonus was assumed to be of cortical origin if the SEPs were pathologically enlarged, and/or if a clear electrical event could be detected in the EEG (back-averaged) which was time-locked to the muscle discharge with a short latency. Details of the electrophysiological technique used for evaluation of myoclonus have been described in previous publications (Hallett *et al.*, 1979; Obeso *et al.*, 1985*b*).

The therapeutic strategy was not uniform for this group of patients. Different drug combinations of clonazepam, sodium valproate, primidone and piracetam were used to control myoclonus. In each patient the minimal number of drugs at the lowest possible dose was given. Generally, patients were hospitalized for initiation of drug therapy, or to introduce major changes in treatment.

Plasma levels of sodium valproate and primidone were measured before and after changes in the therapeutic regimen.

TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS

				Distribution and severity of myoclonus[1]						
Case	*Sex*	*Age when studied (yrs)*	*Disease duration (yrs)*	*Head*	*Trunk*	*Limbs*	*Action*	*Reflex*	*Associated clinical features*	*Diagnosis*
1 (E.A.)	F	55	33	+++	+++	+++	+++	++	None	Posttraumatic
2 (V.O.)	M	52	16	0	++	+++	+++	0	None	Unknown
3 (C.O.)	F	25	2	++	+++	+++	+++	+++	Ataxia	Postanoxic
4 (D.T.)	M	28	2	+++	+++	+++	+++	0	Ataxia	Postanoxic
5 (J.A.)	F	20	10	++	+++	+++	+++	0	Epilepsy	Ramsay Hunt synd.
6 (J.D.)	F	17	13	++	+++	+++	+++	++	Ataxia/epilepsy	Ramsay Hunt synd.
7 (C.G.)	F	68	9	+	+++	+++	+++	++	Ataxia/epilepsy Postural tremor	Ramsay Hunt synd.
8 (F.P.E.)	M	64	11	0	+++	++	++	+++	Ataxia/epilepsy	Ramsay Hunt synd.
9 (M.F.)	M	23	4	++	+++	+++	++	+++	Dementia/epilepsy	Lafora body dis.
10 (J.B.)	F	33	3	0	0	+++[2]	++	+++	Epilepsy	Unknown

[1] 0 = none; + = mild; ++ = moderate; +++ = severe. [2] Myoclonus was confined to the right hand.

RESULTS

The main clinical features of the patients are summarized in Table 1. Action myoclonus of the limbs, trunk and face was the main cause of disability in all patients. Reflex myoclonus to somaesthetic stimulation (electrical, pin prick, touch and/or stretch) of the limbs was observed in 7 patients; these reflex jerks were usually restricted to the stimulated limb, but occasionally were generalized.

SEPs were pathologically enlarged ($> 12\ \mu V$) in all patients and were followed by reflex muscle discharges in the 7 patients with reflex myoclonus. Frequently, one single stimulus elicited a series of repetitive EEG waves and muscle discharges, which in some patients combined to provoke a myoclonic storm. In all patients the EMG discharges were brief (< 50 ms) and the time interval between the electrical stimulus and the reflex jerks was short (around 20 ms in the forearm muscles and 35 ms in the leg muscles). Two patients (Cases 6, 9) showed a photoconvulsive response to flash stimulation at 7–12 Hz. Back-averaging the EEG activity preceding the jerks demonstrated a cortical event time-locked to the muscle jerks in the 7 patients in whom this method was applied. Electrophysiological evaluation thus indicated a cortical origin for the myoclonus in all 10 patients.

TABLE 2. DIFFERENT DRUG TREATMENTS GIVEN TO 10 PATIENTS WITH SEVERE ACTION MYOCLONUS

			Reduction of myoclonus[3]			
Drugs[1]	*No. of patients*	*Dose*[2]	*None*	*Slight*	*Moderate*	*Marked*
Monotherapy		Dose range				
Clonazepam	10	4–12	1	5	4	0
Valproate	7	1000–2000	2	5	0	0
Primidone	3	325–750	0	2	1	0
Piracetam	5	8–18	4	0	0	0
			7	12	5	0
Bitherapy		Maximum dose for each drug				
Clz+valp	6	12/1500	0	4	2	0
Clz+prim	4	12/750	0	2	2	0
Clz+pirc	5	12/15	0	0	4	1
Valp+prim	3	1500/750	0	2	1	0
			0	8	9	1
Polytherapy		Maximum dose for each drug				
Clz+valp+prim	7	12/1500/750	0	0	4	3
Clz+prim+pirc	5	12/1500/18	0	0	2	3
Clz+valp+pirc	2	12/2000/18	0	0	2	0
Clz+valp+prim+pirc	3	12/2000/750/18	0	0	0	3
			0	0	8	9

[1] Clz = clonazepam; valp = valproate; prim = primidone; pirc = piracetam. [2] Dose of each drug is given in mg/day except for piracetam which is expressed in g/day. [3] Scoring system is described in Methods.

However, in some patients more than one pathophysiological mechanism was implicated in the origin of the myoclonus. Thus Case 1 had features of reticular reflex myoclonus in addition to her cortical action and reflex myoclonus (Chadwick *et al.*, 1977).

Table 2 summarizes the antimyoclonic effect of clonazepam, sodium valproate, primidone and piracetam as monotherapy or in different combinations given at different times to the 10 patients. Clonazepam was the most effective drug when given as monotherapy, while the therapeutic effect of piracetam alone in 5 patients with severe action myoclonus was nil or slight.

The final treatment of the 10 patients is summarized in Table 3. In 1 patient it was possible to achieve a marked improvement of myoclonus using two drugs (clonazepam and piracetam), but the greatest benefit in most patients was only possible with polytherapy. Among the different combinations of these drugs used, clonazepam, valproate and primidone in 3 patients, and clonazepam, primidone and piracetam in another 3 patients gave the best results. In the final 3 patients the four drugs had to be given together to achieve dramatic control of the myoclonus.

TABLE 3. FINAL DRUG TREATMENT IN 10 PATIENTS WITH SEVERE ACTION MYOCLONUS

	Treatment[1]				*Time under treatment*	
Case	*Clz*	*Valp*	*Prim*	*Pirc*	*(yrs)*	*Control of myoclonus*
1	6	1200	750	—	6	Maintained
2	6	1200	500	—	1	Maintained
3	3	—	—	15	4	Maintained
4	12	1200	750	15	3	Slight deterioration
5	6	1200	750	—	3	Slight deterioration
6	12	2000	750	18	4	Slight deterioration
7	6	1200	325	18	4	Maintained
8	6	—	325	18	3	Maintained
9	12	—	325	15	2	Maintained until death
10	4	—	750	10	1	Maintained

[1] Dose of each drug is given in mg/day, except for piracetam which is expressed in g/day.

In a few patients it was possible to undertake detailed clinical and electrophysiological analysis of the myoclonus throughout the different phases of treatment. The following case highlights the most important findings.

CASE REPORT (CASE 8)

This 67-yr-old man had a 4-yr history of leg jerks. One cousin died of levodopa-unresponsive parkinsonism, and another had a spastic paraplegia. Initially the jerks were particularly evident when lying in bed or when the feet were touched. He had difficulty in getting to sleep because of jerks elicited by contact with the sheets. A single minimal stimulus (touch or, particularly, pin prick) to the plantar region of either foot provoked a series of jerks of the whole leg which concatenated to produce a salvo of muscle contractions; stretching the toes had similar effects. The patient could not stand or walk. There was no myoclonus of the arms, but there was dysmetria and also a mild degree of bradykinesia. The rest of the neurological examination was normal.

CT brain scan showed mild cerebellar and brainstem atrophy. Routine blood tests, lysosomal enzymes, lactic and pyruvate acid blood levels, and skin and muscle biopsy were all normal. A clinical diagnosis of multiple system atrophy was made on the basis of a positive family history, the clinical signs, and absence of metabolic or enzyme abnormalities, and the CT scan findings.

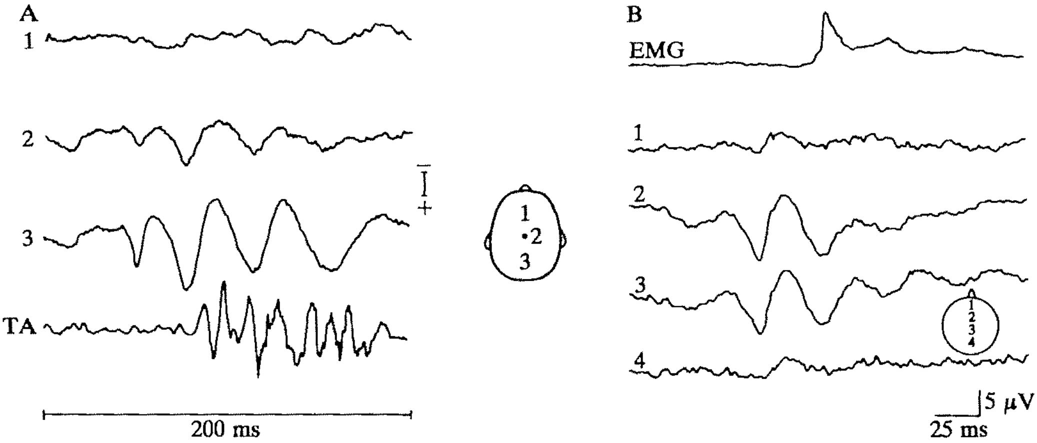

FIG. 1. A, somatosensory evoked potentials (SEPs) (average of 128 responses) (*top 3 traces*) and reflex muscle discharges in left tibialis anterior muscles (TA) (*bottom trace*) following electrical stimulation of the digital nerves of the left hallux (at the beginning of the trace) in *Case 8* before treatment. Calibration bar = 10 μV. B, back-averaging of EEG activity (average of 100 potentials) preceding action myoclonus in left tibialis anterior muscle (EMG, *top trace*). Electrode 2 was at the vertex, electrode 1 was 3 cm anterior and electrode 3 was placed 2 cm posterior to the vertex on the midline; the reference electrodes were linked to the mastoids in this and the following figures.

Electrophysiological evaluation showed enhanced SEPs to digital nerve stimulation of the big toe, and late reflex muscle responses (C reflexes) in tibialis anterior, soleus and foot muscles. The SEPs consisted of four giant waves (> 20 μV) with maximal amplitude over the midline leg area of the sensorimotor cortex (fig. 1A). The initial two spikes of the SEPs were followed with a latency of 28 ms by a reflex EMG discharge in leg muscles; such a temporal relationship was not clearly maintained for the later cortical potentials and EMG bursts. Back-averaging the EEG activity preceding the EMG bursts responsible for the action myoclonus in tibialis anterior muscle showed a large cortical potential over the contralateral sensorimotor cortex with similar morphology to the giant SEPs (fig. 1B).

Treatment with clonazepam (6 mg/day) or piracetam (18 g/day) alone for a week produced a moderate reduction in both the amplitude of the later waves of the SEPs and of the reflex EMG discharges (figs 2A, B), but minimal clinical benefit. Primidone (325 mg/day) alone for a week enhanced the amplitude of later components of the SEPs, with spread of the giant waves to the frontal electrodes (fig. 3A), but reduction of the reflex myoclonus and EEG potentials preceding the jerks (fig. 3B), as well as significant clinical improvement (60% reduction) of both action and reflex myoclonus. At this time, while the patient was receiving oral treatment with primidone, both action and reflex myoclonus showed a dramatic response to the acute administration of clonazepam (1 mg, i.v.). This clinical effect was paralleled by a reduction in the amplitude of the SEPs including

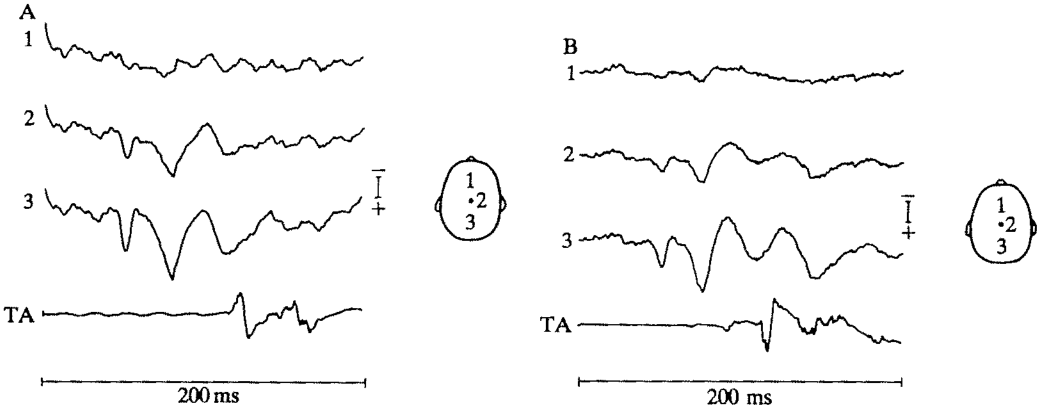

FIG. 2. SEPs and reflex muscle jerks as in fig. 1 in *Case 8* after treatment with (A) clonazepam 6 mg daily, and (B) piracetam, 18 g daily. Either drug given by itself caused a reduction of the repetitive EMG bursts compared with control activity (*see* fig. 1A), but the initial SEP waves are of the same size, although the number of later components is reduced. Calibration bars = 10μV.

the N33-P39-N48 complex, and inhibition of the repetitive later onset spikes with complete abolition of reflex muscle discharges. However, such efficacy was not maintained during chronic treatment (oral) with both drugs at equivalent doses. The combination of piracetam (18 g/day) and clonazepam (6 mg/day) was not effective. Sodium valproate was not well tolerated either in monotherapy (1.2 g/day) or at a lower dose in combination with clonazepam.

The best and most consistently lasting therapeutic result in this patient was achieved with the combination of primidone (325 mg/day), clonazepam (6 mg/day) and piracetam (18 mg/day). On this regime the patient had minimal reflex and action myoclonus. One of the most striking clinical effects was the disappearance of the repetitive EMG myoclonic discharges following cutaneous or stretch stimulation. This dramatic clinical improvement occurred even though the SEPs remained

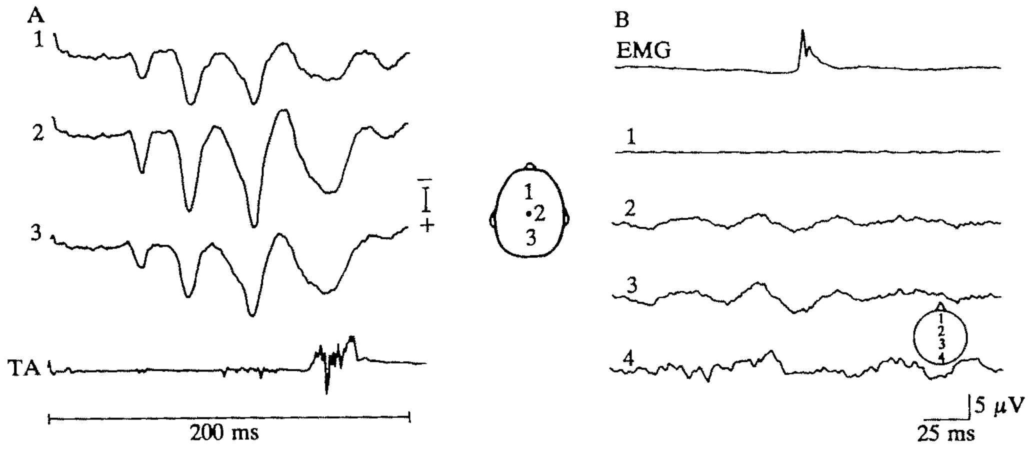

FIG. 3. A, SEPs and reflex muscle jerks as in fig. 2 in *Case 8* after treatment with primidone (325 mg daily). The myoclonus is reduced, but the later components of the SEPs are enlarged, especially at the vertex (*see* fig. 1A). Calibration bar represents 10 μV. B, back-averaging of EEG activity preceding the jerks shows a noticeable reduction in amplitude; and the size and number of EMG discharges are also reduced when compared with control records (*see* fig. 1B).

enlarged and composed of several spikes, albeit restricted to the sensorimotor region. Reflex EMG discharges were abolished (fig. 4).

In summary, this case illustrates how different drugs can have an individual, and an even greater combined action on the different physiological mechanisms underlying cortical myoclonus. The selective actions of such drugs on cortical potentials was also documented in other patients. For instance, clonazepam and piracetam (Cases 3, 7) reduced the amplitude of the primary complex (N20-P25-N33) of the SEPs and associated reflex EMG discharges.

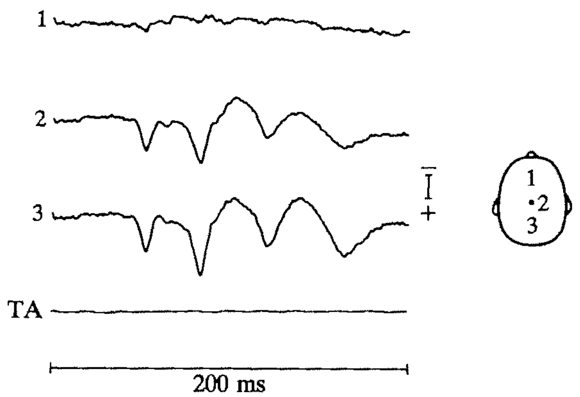

FIG. 4. Recording of SEPs and reflex muscle activity in *Case 8* following chronic oral treatment with clonazepam (6 mg daily), piracetam (18 g daily) and primidone (325 mg daily). The myoclonus is abolished, and the later components of the SEPs are reduced. No back-averaging could be done because the patient had no myoclonus. Calibration bar = 10 μV.

The final therapeutic regimen in each patient is shown in Table 3. In all patients myoclonus was completely controlled, for periods ranging from 1 to 6 years. Two patients (Cases 1, 3), who did not have any other significant neurological deficit, have enjoyed normal motor function ever since their myoclonus was abolished. In the other 8 patients, improvement of motor capability varied from marked to moderate, depending on the severity of their other underlying motor signs such as ataxia or akinesia, and progression of the underlying pathological process. In the 4 patients with the Ramsay Hunt syndrome, probably secondary to a degenerative disease, control of myoclonus has become more difficult over the years. Epileptic seizures were abolished in the patients with a past history of epilepsy.

Side effects in the form of drowsiness, increased ataxia and incoordination, and memory impairment, usually were transient and settled with time. Regular monitoring of blood count, liver and kidney function and routine biochemical blood tests have not shown any abnormality. Plasma levels of primidone and sodium valproate did not vary significantly during the different phases of treatment.

DISCUSSION

Treatment with clonazepam, sodium valproate, primidone and piracetam in different combinations, or the four together, allowed a considerable control of severe action myoclonus in these 10 patients. Clonazepam and sodium valproate have been used together successfully for the treatment of patients with the syndrome of 'myoclonus epilepsy' (Iivanainen and Himberg, 1982; Fahn, 1986*a*). There is one isolated example of a patient with postanoxic action myoclonus in whom good results were achieved with the combination of clonazepam, sodium valproate, piracetam and premarin (Fahn, 1986*a*).

Polytherapy for myoclonus may be necessary in view of its complex pathophysiological origin. Thus in cortical myoclonus several mechanisms may occur in the same patient (Obeso *et al.*, 1985*b*). Transcortical loops mediating stretch and cutaneous (either epicritic, nociceptive, or both) responses are often enhanced, leading to reflex myoclonus (Halliday, 1975; Hallett *et al.*, 1979; Obeso *et al.*, 1985*b*). Motor cortex neurons themselves may be normal, as suggested by the absence of any signs of corticospinal damage in these patients. However, a disorder of interneuronal inhibitory activity in the sensorimotor cortex could allow the recruitment and hypersynchronization of an abnormally large population of cortical motoneurons, as well as an increase in high frequency repetitive firing (Rothwell *et al.*, 1984; Roberts, 1986) in response to afferent impulses from the somaesthetic cortex or from direct projections of the muscle spindles to the motor cortex. In addition, the effect of supplementary motor area and cerebellothalamic projections to the motor cortex before and during movement could also be exaggerated, if the motor cortex inhibitory interneuronal machinery is defective, leading to complex corticosubcortical interactions (Halliday, 1975; Hallett, 1987).

The four drugs used in the patients reported here could act synergistically on the various pathophysiological mechanisms discussed above. However, the detailed study of some of these patients, especially Case 8, distinguished different effects of each of the drugs employed. Thus primidone appeared to act on the motor cortex (efferent side) as it induced a marked improvement in action myoclonus and reduced reflex myoclonus, but the SEPs became larger in amplitude. The latter are thought to represent enhanced hyperpolarization of the soma of pyramidal neurons, between the superficial and deep cortical layers of the sensorimotor cortex (Dinner *et al.*, 1987) where the N20-P25-N33 complex is generated (Rothwell *et al.*, 1984). In contrast, both piracetam and clonazepam usually produced a reduction in the amplitude of the giant SEPs and associated reflex myoclonus. Piracetam was particularly effective against cortical reflex myoclonus (Obeso *et al.*, 1988*b*) perhaps by acting on somatosensory cortex neurons (afferent side). Clonazepam, on the other hand, improved myoclonus of both cortical and brainstem (reticular) origin, and had some therapeutic effect on both action and reflex myoclonus. This suggests that clonazepam may exert multiple pharmacological actions, which might explain why it is the most potent antimyoclonic drug when used in monotherapy. We did not have the opportunity to obtain any precise data on the antimyoclonic activity of sodium valproate in patients with myoclonus.

Most patients with action myoclonus show not only excessive myoclonic discharges, but also silent periods of ongoing EMG activity (asterixis) which contribute to their disability. Neither in this study, nor in the literature, has the effect of antimyoclonic drugs on asterixis been examined specifically.

The need for polytherapy to achieve the most satisfactory control of action and stimulus-sensitive myoclonus also may not have a simple pharmacological explanation. The biochemical pathology of myoclonus is not well defined, which is not surprising in view of the heterogeneity of anatomopathological findings (Hauw *et al.*, 1986) and the diversity of clinical presentation (Fahn *et al.*, 1986; Obeso *et al.*, 1988*a*). It is likely that myoclonus can arise as a consequence of diverse neurochemical abnormalities in the nervous system.

There is now general agreement that the cerebrospinal fluid (CSF) concentration of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin (5-HT), is low in some patients with postanoxic and posttraumatic action myoclonus (Chadwick *et al.*, 1977; Van Woert *et al.*, 1986). Treatment with 5-hydroxytryptophan, the precursor of serotonin, may induce dramatic improvement in some of these patients, suggesting a disorder of 5-HT neurons in the origin of myoclonus following anoxia or head trauma. However, a significant number of patients with postanoxic myoclonus (or myoclonus due to other aetiologies) do not respond satisfactorily to drugs which enhance serotonergic transmission (Chadwick *et al.*, 1977; Fahn, 1986*b*; Van Woert *et al.*, 1986; Giménez-Roldán *et al.*, 1988); nor do all drugs which may improve myoclonus act on serotonergic mechanisms.

Complete control of action and reflex myoclonus cannot be achieved in all patients. However, the success obtained in the patients reported here encourages us to recommend a trial of polytherapy in every case. The main common characteristic of this group of patients is that the abnormal neuronal discharges producing their action and reflex myoclonus appeared to arise in the cerebral cortex. This type of cortical myoclonus, due to a hyperexcitable sensorimotor cortex, is considered a fragment of epilepsy (Obeso *et al.*, 1985*b*; Hallett, 1987). A disorder of GABA inhibitory activity is often postulated to be the mechanism responsible for the origin of focal epilepsy (Meldrum, 1982; Roberts, 1986). Disturbed GABA function could play a significant role in the origin of cortical myoclonus. Indeed, injections into the motor cortex or caudate nucleus in the rat of a GABA antagonist like picrotoxin or bicuculline induces focal myoclonic jerking and localized cortical spike activity, similar to epilepsia partialis continua in man (Jenner *et al.*, 1981; Patel and Slater, 1987). A reduction of 25–50% (compared with control values) of GABA levels has been found in the CSF of patients with postanoxic myoclonus and progressive myoclonus epilepsy (Enna *et al.*, 1979; Airaksinen and Leino, 1982).

Dopaminergic mechanisms do not appear to play a major role in most forms of cortical myoclonus. Dopamine agonists and levodopa have little effect on action and stimulus-sensitive myoclonus of cortical origin, although they can abolish cortical reflex myoclonus to visual stimulation (Obeso *et al.*, 1985*a*).

The cholinergic system has not been generally implicated in the origin of myoclonus (Pranzatelli and Snodgrass, 1985), although cholinergic overactivity has been invoked to explain essential myoclonus or palatal myoclonus because of their occasional response to anticholinergic drugs (Chokroverty *et al.*, 1987; Jabbari *et al.*, 1987).

The contribution of opioids and peptides to the pharmacology of myoclonus is so far limited to observations of beneficial effects of opiates in the syndrome of restless legs with 'myoclonus' and periodic movements of sleep, and infantile spasms (Pranzatelli and Snodgrass, 1985; Walters *et al.*, 1986).

In conclusion, the general pharmacology of cortical myoclonus appears to highlight GABA as the major neurotransmitter likely to be involved.

Among the four drugs we have used to treat the patients reported in this paper, there is substantial evidence to indicate that clonazepam, sodium valproate and primidone act primarily, although not exclusively, by enhancing GABA inhibitory influence (Macdonald and McLean, 1986). Clonazepam facilitates GABAergic transmission by an effect on the benzodiazepine receptor within the GABA receptor-ionophore complex (Olsen *et al.*, 1986). Clonazepam does not have any significant action on serotonin receptors by itself (Jenner *et al.*, 1986), but potentiates GABA inhibition of raphe cell firing (Gallagher, 1978). Although the precise mechanism of action of sodium valproate in patients with myoclonus or epilepsy remains uncertain (Chapman, 1986; Macdonald and McLean, 1986; Van Woert *et al.*, 1986), it does increase GABA levels in nerve terminals, and enhances endogenous GABA postsynaptic activity. Primidone and phenobarbitone produce a postsynaptic increment of GABA-mediated inhibition (Macdonald and McLean, 1986; Olsen *et al.*, 1986) by acting on the GABA receptor-ionophore complex, which contains a modulatory receptor site for barbiturates (Olsen *et al.*, 1986); they also have a presynaptic blocking effect of calcium entry which reduces the release of neurotransmitters. Barbiturates have, in addition, an effect on repetitive neuronal firing by enhancing potassium current outflow (Macdonald and McLean, 1986). The mechanism of action of piracetam is not yet understood, as the effect of piracetam on brain neurotransmitters or modulators has not been identified (Tacconi and Wurtman, 1986), although the molecular structure of piracetam is very close to that of GABA.

The present evidence therefore indicates that GABA and, perhaps, serotonin are the main neurotransmitters involved in the origin of action myoclonus in man. Indeed, postsynaptic GABA-mediated inhibition prevents the effect of abnormal afferent activity to the cerebral cortex and controls pathological enhancement of neuronal output (Meldrum, 1981). A reduction of GABA inhibitory action could play a major role in cortical myoclonus.

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ANTICIPATION IN MYOTONIC DYSTROPHY: FACT OR FICTION?

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SUMMARY

In 1918 Fleischer reported that after transmission from one generation to the next, myotonic dystrophy has an earlier onset and is more severe. The hypothesis put forward by Penrose in 1948 that 'anticipation' is caused by bias of index case selection was based on theoretical arguments only and has not been supported by clinical observations. This hypothesis was tested in a clinical and genetic study of 14 families with myotonic dystrophy. Excluding index patients, an earlier onset in the child was found in 98% of 61 parent-child pairs. A greater mean difference in age of onset was found with transmission via the father than via the mother. The comparison of the severity of the disease between parents and children was difficult because of the variation in symptoms but, in general, the disease was more severe in the child than in the parent. The penetrance of the abnormal gene was nearly complete in the 14 families combined, leaving little room for the observation of 'complementary' parent-child pairs in the future. Also in retrospect no complementary parent-child pairs were found in the first generations. Fertility was severely reduced only in the very early onset patient group and this selective infertility cannot be responsible for the total amount of anticipation observed. It is therefore concluded that anticipation may be inherent in the transmission of myotonic dystrophy. This has important consequences for genetic counselling.

INTRODUCTION

Anticipation in myotonic dystrophy (MD) has been a controversial phenomenon ever since it was described by Fleischer in 1918. The question has never been resolved as to whether the earlier onset and increasing severity of the disease in subsequent generations is inherent to the transmission of the disease, or an artefact caused by biased family studies (Penrose, 1948).

The ophthalmologist Fleischer (1918, 1921–22) reported clinical and genetic studies in 9 families with MD. Five of these had common ancestors, 3 to 5 generations earlier. The disease showed a remarkable evolution in subsequent generations. In the first generations following the common ancestors, neither the

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family history nor early ages of death or a high infant mortality rate indicated the occurrence of MD. After 1 or 2 subsequent generations with patients showing only senile or presenile cataracts, the next generation showed patients with classical MD including muscle weakness and presenile cataracts. In this, and also in the next generation, celibacy, childless marriages, mental retardation and a high infant mortality rate were seen frequently. Fleischer concluded that MD is an inherited degenerative disease with members of the same generation affected in a similar way and at a similar age, with a remarkable absence of the disease in the generations between the common ancestors and the first cataract patients. He argued the disease would become extinct in the families because of the degenerative characteristics in the last generations. Fleischer used nineteenth century concepts of heredity, in which 'degeneration' of families or individuals was a generally accepted notion (Drinka, 1984). The basic principles of modern genetics were not yet generally known. However, he was an astute observer and he performed extensive genealogical studies. His description of 2 mentally retarded children with muscular atrophy and strange talipes can now be recognized as congenital MD. His observations on the sequence of events in MD families still appear to be reliable and were later confirmed by other family studies (Frey, 1925; Henke and Seeger, 1927; Ravin and Waring, 1939; Thomasen, 1948; De Jong, 1955; Klein, 1958). These authors found a dominant pattern of transmission for MD, together with anticipation which they could not explain by mendelian laws.

Penrose (1948) thoroughly influenced opinions on anticipation. In his view, it is an artefact produced by a bias in the methods used in the study of families with hereditary diseases. A family in which the disease occurs in several generations simultaneously is more likely to be studied than a family with only one affected generation. Thus families are selected in which the grandparent is affected late, the parent during middle life and the child at an early age. The reverse situation, grandparent affected at an early age, parent during middle age and child late in life, cannot be observed within a period of sixty years and is unlikely to be recorded. Penrose argued that such 'complementary' parent-child pairs occur as frequently as the anticipating parent-child pairs and that they in due time will cancel out the anticipation phenomenon. This bias of index selection may further be intensified by reduced fertility of patients affected at an early age.

However, complementary parent-child pairs as postulated by Penrose have so far not been recorded. Nevertheless, his hypothesis was readily accepted. Later reports on the earlier onset of the disease in children compared with the parents were usually interpreted as biased observations (Myrianthopoulos, 1963; Bundey and Carter, 1970; Schubert *et al.*, 1980).

Some recent observations again raise the question as to whether anticipation might have a genetic or biological basis. Harper and Dyken (1972) found that congenital MD is transmitted almost exclusively via affected women, which does not fit with simple autosomal dominant inheritance. Pryse-Phillips *et al.* (1982) found anticipation of ages of onset in a large family with complete penetrance of the gene in the later generations, leaving no leeway for the subsequent appearance of late onset cases to form complementary pairs.

The present study was designed to test Penrose's hypothesis. The transmission of MD was studied in 14 families and the results were analysed for three aspects relevant to anticipation. First, the ages of onset and the severity of the disease were compared in parent-child pairs, ascertained without index-patient bias. Secondly, complementary parent-child pairs were sought by collecting data on parents of late-onset patients. The likelihood of their appearance in the future was further examined by calculating the penetrance of the disease in families. Lastly, the fertility of patients was studied to answer the question whether an absence of complementary parent-child pairs might be due to reduced fertility of patients with early onset of the disease.

FAMILIES AND METHODS

The families

When starting the study we had intended to follow simultaneously two approaches to avoid ascertainment bias. (1) The examination of large families with many affected relatives. In this way many parent-offspring pairs would be found per family, and index selection could be prevented by exclusion of the parent-child pairs in which the index patient was involved. (2) The examination of the families of all myotonic dystrophy patients presented within a certain period of time, to prevent selection of a special group of families. Between 1970 and 1977, 51 myotonic dystrophy patients were referred to the neurology department of the Academic Hospital in Rotterdam, of whom 38 were examined personally. We collected names and addresses of their relatives either from the history or from registry offices. It soon became clear that it was not possible to maintain approach (2); a hospital-based study, necessary to detect symptom-free heterozygotes by electromyography (EMG) and slit-lamp examination (Bundey *et al.*, 1970; Polgar *et al.*, 1972), was not possible in the families of 29 preliminary index patients, as many members lived too far from Rotterdam (21 families), refused to cooperate (2), or had died (2). In addition, more preliminary index patients presented than we had expected, exceeding facilities for extensive family studies (4 families). We therefore decided to include only families with many members willing to cooperate and living in or near Rotterdam. These inclusion criteria did not appear to select a special group of families with regard to age of onset and severity of the disease.

Using data from the registry offices we found in 7 instances 2 or 3 index patients to be related. We could therefore draw 14 pedigrees from the remaining 22 index patients. The age at examination of the 22 index patients varied between 0 and 69 yrs. Starting from the near relatives of index patients and proceeding through branches of the family where we expected from the history to find MD, we examined 264 relatives in these 14 families; 30 relatives were examined at home. We included the data of 6 deceased patients and 4 patients living far away, in whom the disease had been diagnosed and documented by a neurologist or an ophthalmologist.

Methods

Historical data. The age of onset was established from the history. We defined in advance four characteristic onset patterns: (1) painless muscular cramps (slow relaxation after contraction) of the hands; (2) muscular weakness of face, pharynx, neck or distal limbs; (3) deterioration of vision caused by cataracts; and (4) the syndrome of congenital MD comprising respiratory distress, swallowing problems, hypotonia and stiff joints, in an infant of a mother with MD. Other signs, such as loss of hair, bowel complaints, irregular menses and mental inertia were regarded as too nonspecific to accept as symptoms marking the onset.

A number of patients could not recall precisely the onset of symptoms by year. We therefore recorded the onset by decades. By carefully questioning patients on the beginning of their first symptom and helping them to relate this to significant life events such as school years, marriage data, birth of children, etc., determination of the onset in decades proved to be possible in all patients. If a patient could not supply onset data himself we questioned a close relative. Congenital MD was classified as onset in decade 0 in order to distinguish these patients from those with childhood-onset without neonatal symptoms. In symptom-free patients the age at examination was considered to be the age of onset, if clinical signs of MD were found. If only subclinical abnormalities were found (electromyographic myotonia or myotonic cataracts without impaired visual acuity), the age at examination plus 5 yrs was considered to be the age of onset (Bundey and Carter, 1972).

Historical data on the parents who transmitted the MD gene to the members of the oldest examined generation were collected from their children and, when available, from medical records.

Physical examination. A general and neurological examination was performed in all relatives examined in the hospital. In patients seen at home a limited neurological examination proved to be sufficient to obtain data concerning myotonia and muscle weakness.

Electromyography. This was performed with a standard electromyograph (Disa) and concentric needle electrodes. Myotonia was exclusively sought, in order to cause as little discomfort as possible. Usually only the abductor pollicis brevis muscle was examined, but sometimes also the extensor digitorum communis muscle of the forearm. Myotonic discharges were diagnosed if spontaneous electrical discharges with the characteristic waxing and waning of frequency and amplitude were seen or heard.

Slit-lamp examination. For slit-lamp examination in the hospital a standard fixed slit-lamp (Haag-Streit) was used. A high resolution portable slit-lamp (Kowa) was used in 14 of the 30 relatives examined at home. Mydriatics were not administered as the examination was performed in a dark room. A diagnosis of myotonic cataract was made if, in the anterior or posterior cortex, fine white dust-like opacities were found interspersed with a sufficient number of iridescent coloured opacities. Since no quantitative criteria appear to exist we arbitrarily took a number of 10 coloured opacities as a minimum for diagnosis.

Diagnostic criteria. MD was diagnosed if one or more of the following characteristics were established: (1) clinical or electromyographic (EMG) myotonia; (2) muscle weakness in those groups of muscles characteristically affected by MD; equivocal signs, such as mild atrophy of temporal or hand muscles, were disregarded if they occurred in isolation; (3) myotonic cataract; (4) the syndrome of congenital MD in infants. In family P (family S+ST in Höweler *et al.*, 1980), myotonia congenita was found in some relatives. For the present study these relatives were considered normal and MD was only diagnosed if other signs were present apart from myotonia.

RESULTS

The families

The 14 families are presented in pedigrees A-P (figs. 1-4). Five families consisted of several branches, each with its own index patient, and linked by genealogical studies (families A, F, G, N, P). A further 2 families consisted of one main branch, supplemented by a small second branch indicating a common ancestor (families H and L). Altogether 264 individuals were examined, 133 had MD, 127 were normal; in 4 individuals the diagnosis was dubious. Detailed information on the family members examined is given elsewhere (Höweler, 1986).

Not all relatives were studied by each of the three methods of examination. Table 1 gives the number of individuals diagnosed as affected, normal and dubious with the methods applied. Whenever relatives were found to be normal on clinical

TABLE 1. DIAGNOSIS AND METHODS APPLIED IN 264 INDIVIDUALS

	Clinical examination and investigations					
Diagnosis	*Slit-lamp EMG*	*Slit-lamp*	*EMG*	*Clinical examination only*	*Diagnosis from reports*	*Total*
Affected	79 (59%)	26 (20%)	4 (3%)	16 (12%)	8 (6%)	133
Normal	102 (80%)	14 (11%)	1 (1%)	8 (6%)	2 (2%)	127
Equivocal	4 (100%)					4
Total	185	40	5	24	10	264

Symbols for figs 1-14

$\overset{6}{\blacksquare}$ Male, myotonic dystrophy, onset in the sixth decade

○ Female, normal

⧄ Deceased

☐ Normal, children not examined

⍰ Diagnosis of myotonic dystrophy dubious

⊟ Not examined

◇ 3 sibs, not examined

➡ Index patient

⧄ Perinatal death after gestation > 7 months, medical reports suggestive of congenital myotonic dystrophy

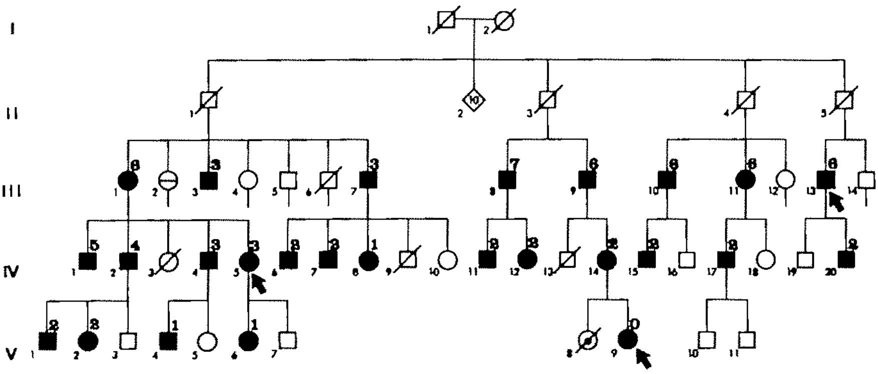

FIG. 1. Family A.

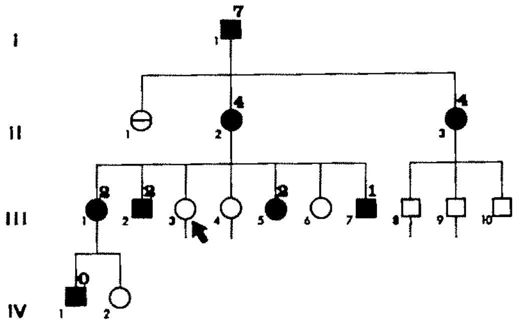

FIG. 2. Family B.

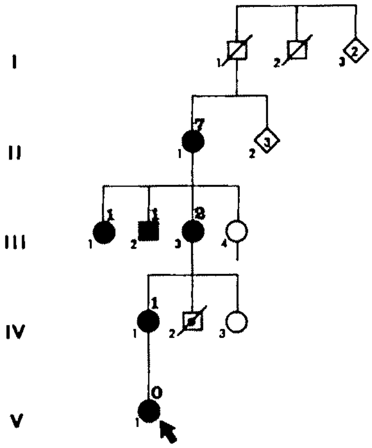

FIG. 3. Family C.

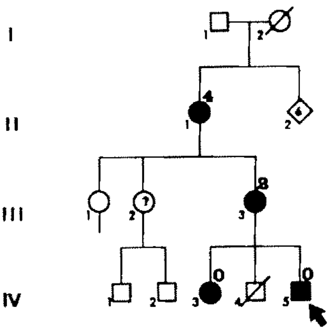

FIG. 4. Family D.

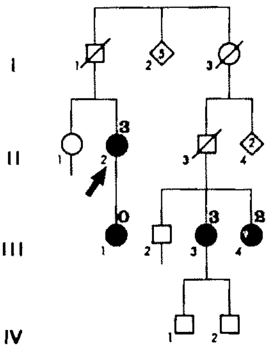

FIG. 5. Family E.

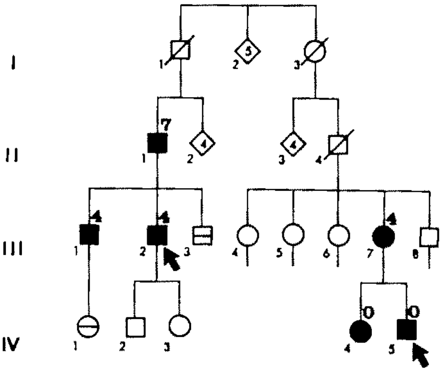

FIG. 6. Family F.

examination, efforts to complete the examination were made. In 80%, slit-lamp and EMG examinations were performed, and in another 11%, a slit-lamp examination. In spite of the application of all three methods, the diagnosis in 4 relatives remained dubious: 3 had only white opacities or only a few coloured opacities on slit-lamp examination (H-IV-1, L-IV-3 and L-V-13) and D-III-2 had absent ankle jerks.

The number of complete examinations was smaller in the affected individuals (59%). EMG was omitted in patients who were afraid of the procedure, when clinical myotonia was present. Eight patients had had cataract operations, making slit-lamp examination uninformative. In more than 80% of the affected individuals the clinical diagnosis was confirmed either by slit-lamp or EMG examination.

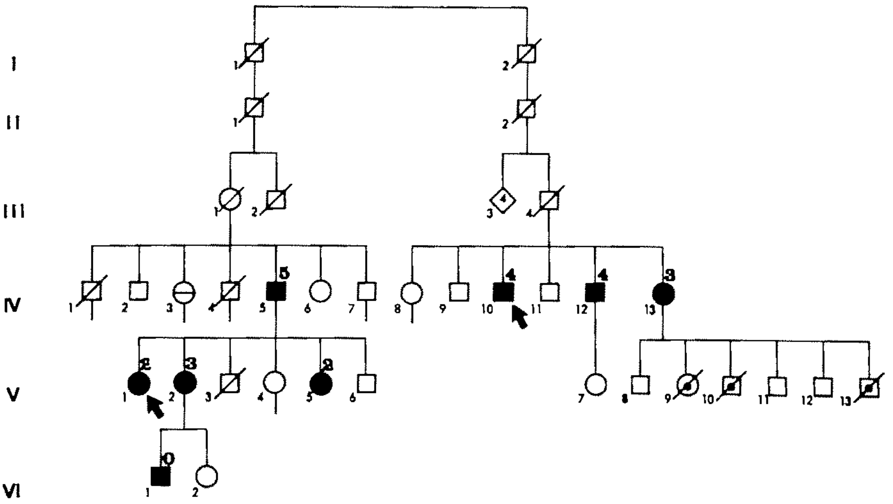

FIG. 7. Family G.

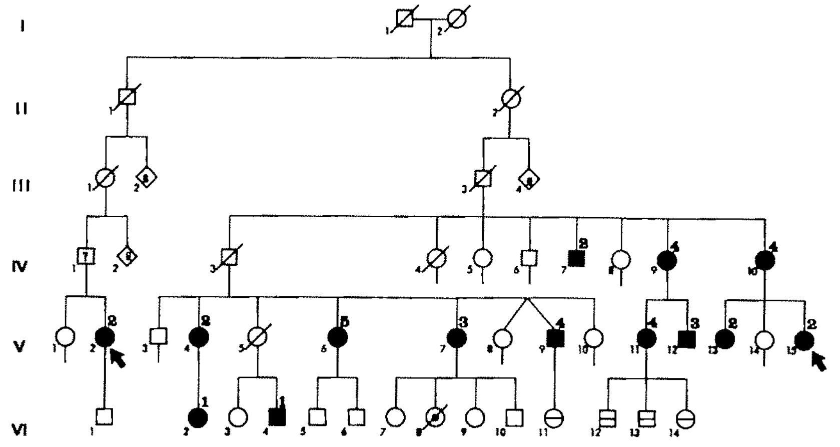

FIG. 8. Family H.

Thirteen (10%) affected relatives had no muscle abnormalities. On slit-lamp and EMG in 8 of them, both myotonic cataracts and EMG myotonia were found, in 3 only myotonic cataracts and in 2 only EMG myotonia. In the 14 families we found 13 patients with congenital MD. Furthermore, polyhydramnios documented in the medical records on 12 perinatally deceased children allowed the conclusion that they probably were affected. In all these cases the mother was the transmitting parent.

Age of onset in parent-child pairs

For each MD patient the decade of onset is given in the pedigrees in bold numbers at the right upper side of the symbol. In all but 1 case the onset in the

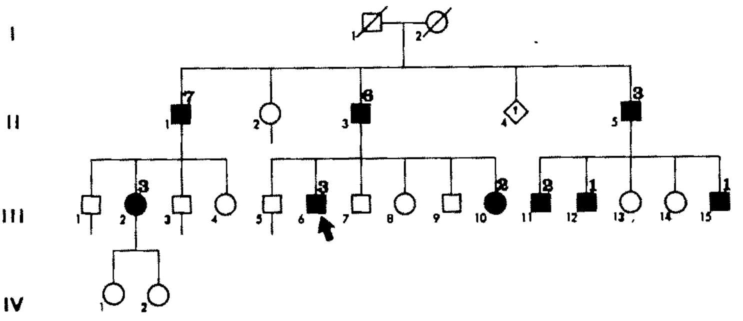

FIG. 9. Family J.

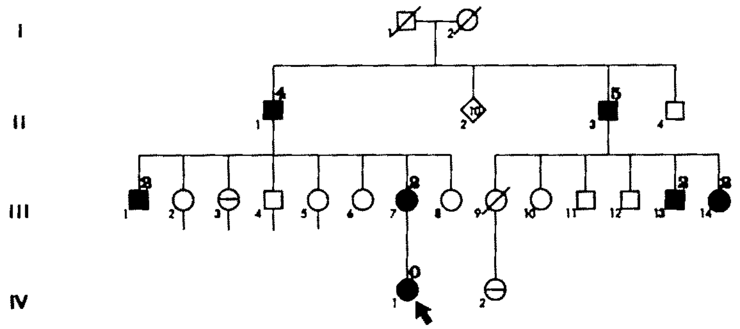

FIG. 10. Family K.

child was one or more decades earlier than in the transmitting parent. The only exception is parent-child pair H-IV-9/H-V-11, in which both parent and child gave a history of onset in the fourth decade. We suspected, however, that the stated age of onset of H-IV-9 was possibly too early, since she showed no abnormal signs other than myotonia at the time of examination, which was 27 yrs after the onset that she gave for this symptom.

In several instances the classical 3 generation sequence of senile, adult and childhood onset was found (e.g., A-III-9, A-IV-14 and A-V-9; G-IV-5, G-V-2 and G-VI-1; P-III-21, P-IV-13 and P-V-2). In 2 instances the disease was found in 4 generations (families B, C). More often MD was found in only 2 generations. Usually either the transmitting grandparent had already died (e.g., E-I-1), or the child had no offspring (e.g., J-III-6).

In 4 branches of a family, MD was found only in 1 generation (second branch of families E, G and L; first branch of family H). If the genealogical connection with the other branches of the family had not been found a dominant transmission pattern would not have been obvious. A remarkable observation was that in some families' anticipation of ages of onset did not run parallel in different branches. In family A the children of A-III-7 had ages of onset in the same decades as the grandchildren of his sister A-III-1. Similarly, in family C patients

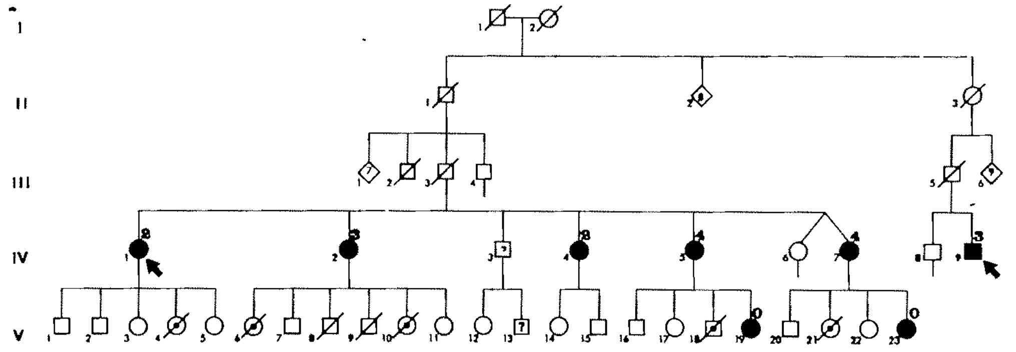

FIG. 11. Family L.

TABLE 2. AFFECTED PARENT-CHILD PAIRS AND MEAN DIFFERENCES OF AGES OF ONSET IN DECADES BY SEX

	No. of pairs	*Mean differences of ages of onset in decades*	*Range of ages of onset in decades*
Father-son	24	3.20	1-5
Father-daughter	19	3.47	2-5
Mother-son	15	2.60	1-6
Mother-daughter	20	2.45	0-6

were seen with ages of onset in the first decade in generation III as well as in generation IV.

We found a total of 78 parent-child pairs with MD. After exclusion of the parent-child pairs involving an index patient, 61 pairs remained. In 60 of those (98%) the child had an earlier age of onset than the transmitting parent. The mean difference in age of onset was 2.9 decades (range 0–6 decades).

Subsequently, the influence of the sex of the parent or the child was studied. In Table 2 the differences in ages of onset are recorded according to the sex of parents and children. In this table the index patients have been included as there were as many males as females. The mean differences in ages of onset appeared to be greater when the father was the transmitting parent. On applying the median test with χ^2 the differences between pairs with a transmitting father and pairs with a transmitting mother was significant ($P < 0.01$). The sex of the parent thus appeared to influence the difference of the ages of onset. However, this is probably not the only influence, since the range of the differences is wide for both sexes.

Severity of MD in parent-child pairs

It proved impossible to compare exactly the severity of the disease in parents and children. They often had different symptoms and signs, for example, only

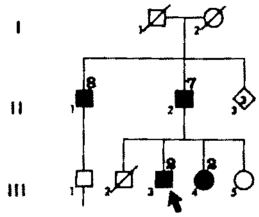

FIG. 12. Family M.

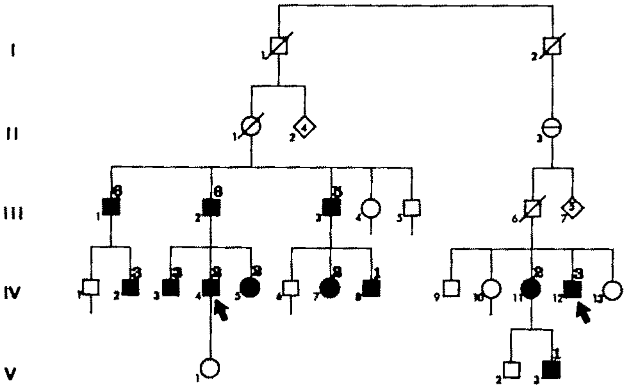

FIG. 13. Family N.

cataracts or only muscle weakness. Furthermore, a parent and child often had the same symptom for a different period of time, such as muscular weakness that had been progressive for many years in one, the other having only mild weakness of recent onset. In general, we found the clinical picture to be related to the age of onset. Patients with an age of onset over 50 yrs usually had cataracts as their main sign, muscle weakness, usually mild, developing only late in the disease. Patients with early adult onset (10–30 yrs) commonly had muscle weakness as their main symptom, with cataract and mental changes appearing in later stages. With congenital or childhood onset (< 10 yrs), mental symptoms were usually moderate to severe with muscle weakness as milder symptom when the neonatal symptoms had subsided. Thus parallel to the decreasing age of onset in subsequent generations, we observed a sequence of symptoms in subsequent generations with cataracts in the grandparents, 'classical' MD in the parent and mental retardation with muscle weakness in the child.

Penetrance of the MD gene

When penetrance is complete, 50% of the children of gene carriers are expected to show signs of the disease. Calculating the penetrance of the disease only makes sense if all the descendants of a gene carrier are examined. In the 14 families some generations or sibships could be only partially examined, since some individuals had died or did not wish to be examined. We therefore calculated the penetrance in those generations and sibships where 50% or more of the family members had been examined. The index patients were eliminated from the calculations. Relatives who presented dubious abnormalities were considered to be normal. The deceased or unexamined family members were not included (38 individuals = 13%).

In Table 3 the numbers of offspring with MD are given, together with normal progeny. In the 14 families combined, the calculated percentage of children showing signs of the disease was 46%. In the presence of complete penetrance this

TABLE 3. χ^2 ANALYSIS OF PENETRANCE OF MYOTONIC DYSTROPHY, BY FAMILY AND ALL FAMILIES COMBINED

Family	*No. of children of gene carriers*		χ^2
	Affected	*Normal*	
A	23	13	2.78
B	7	7	0.00
C	4	2	0.67
D	2	4	0.67
E	3	4	0.14
F	3	6	1.00
G	6	13	2.58
H	12	15	0.33
J	8	12	0.80
K	4	8	1.33
L	6	15	3.86
M	1	2	0.33
N	10	9	0.05
P	13	12	0.04
Total	102 (46%)	122 (54%)	1.79

percentage should have been 50. Based on this expectation the χ^2 value was calculated, from which it could be concluded that the penetrance of the gene was not significantly different from expectation ($0.10 < P < 0.20$). In order to detect interfamilial differences the same procedure was undertaken for the individual families. Penetrance seemed incomplete in only one instance (family L). However, the difference from expectation is barely significant ($P < 0.05$) and therefore this result should be treated as a chance finding. Furthermore, it should be pointed out that in this family (and in family G) a higher percentage of patients would have been found if the children who had probably died of congenital MD had been included in the calculations. Finally, the homogeneity of the results between families was calculated. This was done by taking the difference between the sum of the separate χ^2 values for the individual families and the χ^2 value for the summated data. This gives a χ^2-value of $14.58 - 1.79 = 12.79$ (df = 13), $P < 0.50$, which means that the data are homogeneous with respect to the accordance with the expectation of 50% penetrance. Therefore the penetrance analysis suggests that it is almost impossible that a sufficient number of complementary parent-child pairs will appear in the future to cancel the anticipation observed in these families.

Complementary pairs in retrospect

If complementary pairs had existed in the past, it should be possible to find them retrospectively. It would be expected that patients with a late onset of the disease would remember having had a parent with earlier onset and more

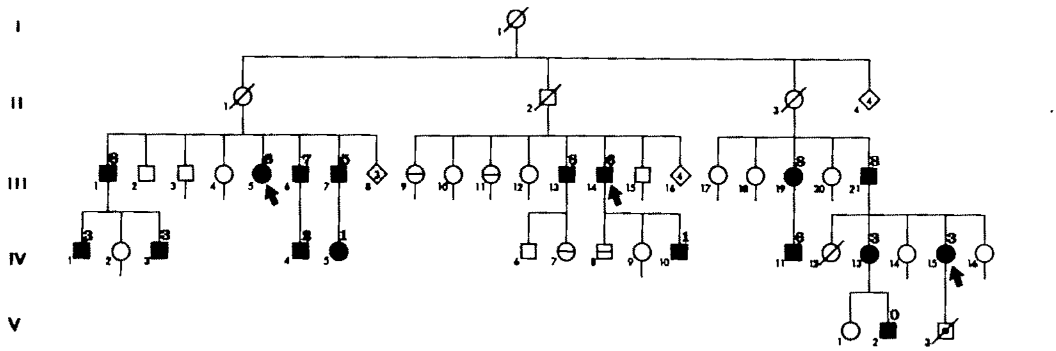

FIG. 14. Family P.

severe MD. We therefore collected historical data on the parents who transmitted the disease to the members of the oldest examined generation. Twenty-five individuals must have transmitted the abnormal gene to the different branches of the families. In 20 cases the transmitting parent could be detected by the genealogical data. In 4 families this was not possible, so we collected data on both parents. Data on the parents of Case B-I-1 were not available. Table 4 presents the collected information on these transmitting or potentially transmitting parents. Two were still living and were examined (D-I-1 and H-IV-1).

Based on the description of the symptoms according to their children, we presumed that 19 parents had not had clinical MD; 7 had had late onset MD with cataracts as the sole or main sign. Two parents had had the first symptoms in the fifth decade (L-III-3 and L-III-5); their children had an age of onset between the second and fourth decades. Thus the historical data on the parents who transmitted the disease to the members of the oldest examined generation in these 14 families did not show complementary parent-child pairs in retrospect.

The family history indicated that 2 patients of the oldest examined generation had had a deceased uncle with a presumed age of onset of MD earlier than their own (C-I-2, before the sixth decade; C-II-1, seventh decade; L-III-2, third decade; L-IV-5, fourth decade). This probably indicates nonparallel anticipation of onset ages in different branches of the family. A similar situation was found in family A, where the anticipation of the age of onset did not run parallel in different branches of the family (e.g., A-IV-1 with his uncle A-III-3). These cases also illustrate that it is fully possible to detect MD retrospectively in deceased members of a previous generation, and thus to detect complementary parent-child pairs if they had occurred.

It might be supposed that new mutations occurred in the oldest examined generation. However, genealogical data often revealed connections with other branches of the family, indicating the prior presence of the mutation. Furthermore, cataracts were reported in 8 parents of patients in the oldest examined generation, suggesting they were heterozygotes. It may be concluded that in the 9 families

TABLE 4. DATA ON THE TRANSMITTING PARENTS

Transmitting parent	*Age at examination or age at death (yrs)*	*Description of symptoms by their children*	*Presumptive diagnosis*
A-II-1	80	Cataract operation aged 78, no muscle weakness	Senile onset MD
A-II-3	92	Cataract since aged 80, no muscle weakness	Senile onset MD
A-II-4	70	No cataract or muscle weakness	No clinical MD
A-II-5	80	Cataract operation aged 67, no muscle weakness	Senile onset MD
C-I-1	59	No cataract or muscle weakness, sudden death	No clinical MD
D-I-1	83	On examination nonspecific lenticular opacities, no muscle weakness	No clinical MD
D-I-2	35	Died of postpartum thrombosis, no muscle weakness	No clinical MD
E-I-1	68	No cataract or muscle weakness, died of diabetes	No clinical MD
E-II-3	45	No cataract or muscle weakness, sudden death	No clinical MD
F-I-1	70	No cataract or muscle weakness, died of war injuries	No clinical MD
F-II-4	58	No cataract or muscle weakness, died of renal failure	No clinical MD
G-III-1	46	No cataract or muscle weakness, died of gall bladder disease	No clinical MD
G-III-4	56	No cataract or muscle weakness, died of a stroke	No clinical MD
H-IV-1	71	On examination nonspecific lenticular opacities, no muscle weakness	No clinical MD
H-III-3	79	Cataract operation aged 68, no muscle weakness	Senile onset MD
J-I-1	86	Cataract since age 80, no muscle weakness	Senile onset MD
J-I-2	84	No cataract or muscle weakness	No clinical MD
K-I-1	67	No cataract or muscle weakness, died of bladder disease	No clinical MD
K-I-2	77	No cataract or muscle weakness	No clinical MD
L-III-3	48	Cramps in hands and muscle weakness, died of glioblastoma	Late adult onset MD
L-III-5	51	Cataract aged 48, no muscle weakness, sudden death	Late adult onset MD
M-I-1	66	No cataract or muscle weakness	No clinical MD
M-I-2	90	No cataract or muscle weakness	No clinical MD
N-II-1	75	Cataract operation aged 65, later walking problems	Senile onset MD
N-III-6	57	No cataract or muscle weakness, sudden death	No clinical MD
P-II-1	77	Cataract operation aged 55, rheumatism since age 64	Senile onset MD
P-II-2	71	No cataract or muscle weakness	No clinical MD
P-II-3	76	No cataract or muscle weakness	No clinical MD

TABLE 5. NUMBER OF CHILDREN OF MD PATIENTS AGED OVER 20 YRS, BY ONSET DECADE AND BY SEX. CHILDREN DECEASED IN THE PERINATAL PERIOD, AFTER A GESTATION OF > 28 WEEKS, ARE INCLUDED

	All patients		*Males*		*Females*	
Onset decade	*n*	*Mean no. of children*	*n*	*Mean no. of children*	*n*	*Mean no. of children*
0	0	—	0	—	0	—
1	7	0.13	4	0.00	3	0.33
2	31	0.80	12	0.25	19	1.15
3	22	1.81	12	1.00	10	2.80
4	16	2.93	7	2.28	9	3.44
5	6	3.00	5	3.20	1	2.00
6	12	2.41	9	2.44	3	2.33
7	7	3.00	6	2.83	1	4.00
8	4	2.50	3	3.00	1	1.00
Total	105	1.82	58	1.63	47	2.06
Normal sibs	84	1.75	39	1.48	45	1.97

where the transmitting parent was indicated by genealogical data (families A, C, E, F, G, H, L, N, P) the MD gene probably was already present in the parents of the oldest examined generation.

Fertility of MD patients

If MD affected the fertility of the patients in such a way that only patients with a late age of onset had children and patients with an earlier onset age were infertile, anticipation might be a secondary effect of selective infertility. We studied the fertility of the patients, grouped per decade of age of onset. Since testicular atrophy is frequently found in affected men, fertility was also calculated for each sex. The results are given in Table 5. For comparison, we also calculated the fertility of the normal sibs. The fertility of all patients together was slightly higher than the fertility of the normal sibs.

The fertility of male and female patients combined was higher than the fertility of the normal sibs when the age of onset was over 20 yrs (third to eighth decades), and lower with age of onset in the first and second decades. Nearly zero fertility was found only with ages of onset in the first decade. However, male patients with onset in the first, second and third decade had reduced fertility as compared with female patients, already approaching zero with onset in the second decade.

The question thus arises as to whether this diminished fertility may have caused the anticipation in these families. Assuming a normal fertility of 1.48 (mean fertility of normal brothers), the male patients with an onset in the first, second and third decades would have had a further 26 children if their fertility had been normal $(4\times 1.48+12(1.48-0.25)+12(1.48-1.00))$. Assuming a normal female fertility of 1.97, the female patients with an onset in the first and second decades would have had a further 20 children if their fertility had been normal. Thus with normal fertility, another 46 children would have been born in these families, of whom 23 would have carried the abnormal gene. If anticipation is an artefact, the age of onset is variable at random and only a limited number of these 23 children would have had a late onset. But even if all would have had a late onset and thus would form complementary pairs with their parents, there would be only 23 complementary pairs, far below the 60 anticipated pairs observed in the study. These data show strongly reduced fertility only in patients with a very early onset of the disease. This effect appears to be too small to be responsible for the total amount of anticipation observed.

DISCUSSION

In 60 of 61 (98%) parent-child pairs ascertained without bias, the ages of onset of MD were one or more decades earlier in the children than in the parents. This is in agreement with most previous family studies (Thomasen, 1948; Klein, 1958), which were never considered conclusive, since selection of index patients might have caused the anticipation phenomenon. In this study the parent-child pairs involving an index patient were excluded so that index selection could not be the cause of the anticipation of ages of onset.

A changing pattern of symptoms was found with decreasing age of onset. Therefore the severity of the disease could not be quantitated in parent-child pairs. Usually cataract was the main symptom with senile age of onset, muscle weakness with young adult onset and mental symptoms and muscle weakness with childhood onset. Assuming that mental symptoms are more disabling than muscle weakness, and that muscle weakness is more disabling than cataracts, it may be concluded that MD is usually more severe in the child than in the parent. The penetrance in the 14 families combined was not significantly different from expected. If in the future many complementary parent-child pairs would appear, the percentage of patients in the families would be far beyond the expected 50%. Furthermore, complementary parent-child pairs were not found in retrospect. The occurrence of complementary parent-child pairs, as assumed by Penrose, must therefore be very rare.

Strongly reduced fertility was found only in the group of patients with a very early onset of the disease: in women with onset in the first decade, and in men with onset in the first and second decades. With a later age of onset, fertility was diminished only moderately or was normal. It therefore seems improbable that the observed anticipation is caused by the fact that only patients with a late onset of the disease have offspring, as was suggested by Thomasen (1948) and Penrose (1948). Thus we found no support for the hypothesis that anticipation in MD is caused by bias of ascertainment. Anticipation appears to be inherent in the transmission of MD.

In general our results are in agreement with the observations of Fleischer (1918, 1921-22). The following pattern of transmission emerged. After a mutation which may have occurred several generations earlier, myotonic dystrophy can be observed in different branches of a family in 1 to 4 generations, with decreasing ages of onset and increasing clinical manifestations in subsequent generations. Follow-up studies are needed to determine whether the disease will disappear from the family in the generation following the childhood-onset generation.

The exclusive maternal transmission of congenital MD may be related to the anticipation phenomenon. Harper and Dyken (1972) explained the exclusive maternal transmission by assuming the existence of an intrauterine toxic factor influencing the child carrying the MD gene. They did not find a difference in fertility between male and female patients. However, they studied the fertility of patients of all age groups combined. In this study we found a decreased fertility of men in comparison with women when affected in the second and third decades. This difference in fertility in early adult onset patients, combined with anticipation, contributes to the exclusive maternal transmission of congenital MD.

Some methods used in this study may raise questions. Since the index patients were derived from a larger group of preliminary index patients it may be wondered whether the 14 examined families constitute a selected group. In our opinion the inclusion criteria used did not select a special group of families with regard to age of onset and severity of the disease. To check this we compared the available data on the included and the nonincluded preliminary index patients. Between the two groups no statistical differences were found for the mean age at presentation (Student's t test $0.10 < P < 0.20$) or the sex (χ^2 $0.30 < P < 0.50$). The ages of onset were known only for 16 of the 29 nonincluded preliminary index patients. No difference was found between the mean age of onset of the 16 nonincluded (2.50 decades, SD 1.26) and the 21 included index patients (2.66 decades, SD 1.85). As the severity of MD is related to the age of onset, it is unlikely that we selected the index patients on this criterion. Furthermore, in 15 cases an affected parent or child of a nonincluded preliminary index patient was examined. With no exception, the age of onset of the child was earlier than the age of onset of the transmitting parent. These data do not indicate that a special group of index patients was chosen for this study.

Some authors (Lynas, 1957; Schubert *et al.*, 1980) have stated that it is not possible to determine the age of onset of MD reliably on the basis of historical data. This might apply when using too specific time criteria to measure the age of onset, or when using ill-defined marking symptoms. In our opinion the methods used in this study (defined criteria for the onset, applied by one examiner; decades instead of years as the measure for the onset) are sufficiently reliable to compare the age of onset in different patients. Another point may be whether different symptoms are equally acceptable to establish the age of onset of the disease, since the presenting symptom may differ in different patients. However, after a longer duration of the disease most patients also develop the other main symptoms.

The mechanism of anticipation is difficult to explain. When the expression of a gene changes in successive generations, it might be that the mutation itself changes from generation to generation, or that an additional factor influences the expression of the abnormal gene. Little is still known as to the factors that influence the expression of genes. In this study we found a greater difference in ages of onset when the father was the transmitting parent. In this respect MD somewhat resembles Huntington's disease, where the juvenile form has a paternal origin. In looking for additional factors, both genetic and environmental influences must be considered. The genetic factors can be divided into the effect of a second allele at the same locus, transmitted by the normal parent, or the action of different genes at one or more other loci. If these genetic factors themselves are transmitted in a mendelian fashion, variable effects would be expected rather than the progressive severity of the disease. Apart from theoretically possible but unexplained immunological mechanisms, a gradual change of the mutation itself in successive generations might be assumed, provoked by environmental factors or by the meiotic process. The mechanism operative during meiosis might resemble that postulated for the transition of the premutation of the fragile X syndrome to the active gene mutation (Pembrey *et al.*, 1985; Ledbetter *et al.*, 1986). Alternatively, the first change may be an epigenetic defect which, instead of being eliminated, is fixed in the genome during subsequent meiosis and leads to an accumulation of defects during the following generations. In this respect heritable changes in DNA-methylation (Holliday, 1987) might be contemplated. Finally, gene conversion could be operative in these situations (Kourilsky, 1986). The recent localization of the MD gene on chromosome 19 (Whitehead *et al.*, 1982) opens options for isolation and cloning of the gene. Thereafter, further studies at the DNA level to assess whether patterns of methylation influence the expression of the MD gene might be undertaken.

If anticipation is inherent in the transmission of MD, this will have consequences for genetic counselling. Patients should be informed that their affected children are likely to have a more severe form of the disease than they have themselves, with onset at an earlier age and a reduced chance of an independent life because of the mental symptoms of congenital or childhood-onset MD. This does not only apply to women who already have a child with congenital MD (Grimm and Harper, 1983; Glanz and Fraser, 1984), but to all patients, even when they have only mild symptoms themselves. This information is important since modern linkage studies allow prenatal diagnosis of MD (Lunt *et al.*, 1986) and selective abortion may be offered to parents.

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HAND AND SEX DIFFERENCES IN THE ISTHMUS AND GENU OF THE HUMAN CORPUS CALLOSUM

A POSTMORTEM MORPHOLOGICAL STUDY

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SUMMARY

The midsagittal area of the corpus callosum was measured in its entirety and in seven subdivisions in a sample of 50 brains consecutively obtained from autopsies of individuals who had neuropsychological testing before death. A 12-item test of hand preference was used as an index of the pattern of interhemispheric functional asymmetry. Callosal size was analysed for two factors: hand preference, classified as consistent-right-hand preference (CRH) versus non consistent-right-hand preference, and sex. The group of nCRH (n = 18) was found to have a larger overall callosal area, with the greatest difference occurring in the posterior body segments, especially the isthmus. The isthmus probably includes interhemispheric fibres from posterior parietal and superior temporal cortex which involves cortical regions related to functional asymmetry. The results of variation in callosal morphology are discussed as part of a possible substrate of functional asymmetry and due to variation in axonal elimination in early brain development.

Sex differences were found in several aspects of callosal anatomy. (1) The difference between hand groups in the posterior body occurred in interaction with sex: handedness was a factor in callosal size in males (n = 15), but not in females (n = 35). This result is consistent with the general hypothesis of females having less clear lateralization than males. (2) Females did not have a larger overall callosum or a larger splenium, either in absolute size or size proportional to brain weight. The latter measure was considered since callosal area correlated with cerebrum weight (r = 0.48). In contrast, females of both hand groups were found to have a larger proportional isthmus compared to CRH males. (3) Of all callosal regions, only the genu and a part of the anterior body were found to be larger in absolute size in males than females. (4) Callosal size decreased with chronological age in males, but not in females.

INTRODUCTION

Functional specialization of the cerebral hemispheres is a well documented feature of brain organization in man, based both on clinical and experimental studies (e.g., Heilman and Valenstein, 1985; Bryden, 1982; respectively), but its biological

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basis is unknown. The facts that functional asymmetry in man is (1) consistent in direction and prevalence across groups and (2) present soon after birth (Witelson, 1987) suggest that functional asymmetry is dictated, at least in part, by genetic or epigenetic factors. Numerous right-left neuroanatomical asymmetries have been described since functional asymmetry was first noted more than a century ago (e.g., reviews in Witelson, 1977, 1983; LeMay and Geschwind, 1978; Galaburda, 1984), but it is not yet established whether the neuroanatomical asymmetries form part of a biological substrate of functional asymmetry.

Individual differences exist in the direction and magnitude of functional asymmetry. Although speech lateralization and hand preference are far from perfectly correlated, left handers as a group have a higher prevalence of right-sided or bilateral language representation compared with right handers and also have a greater degree of bihemispheric representation of language, that is, less marked functional asymmetry (Bryden, 1982; Beaton, 1985). There may even be variation among right handers (Levy *et al.*, 1983; Witelson, 1983, p. 136). In addition, many studies have indicated that females have greater bilateral representation of cognitive functions, although some results are inconsistent (Beaton, 1985). A correlation between variation in neuroanatomical asymmetry and variation in behavioural measures known to be correlated with functional asymmetry, such as hand preference, would support the hypothesis that neuroanatomical asymmetry is a basis of functional asymmetry. Such evidence is beginning to accumulate and currently more than a dozen studies have been reported concerning the correlation between measures of functional asymmetry (such as hand preference, dichotic ear asymmetry, speech lateralization by the Amytal test, or lesion studies) and measures of anatomical asymmetry (mainly in vivo measures of hemisphere breadths and sylvian fissure angulation). There are inconsistent results, but overall they support a correlation between gross anatomical asymmetry and functional asymmetry. These studies are reviewed elsewhere (Witelson, 1980; Witelson and Kigar, 1988*a*).

The corpus callosum is the main fibre tract connecting the cortical regions of the right and left hemispheres and, accordingly, may be a component of any neuroanatomical substrate of hemisphere specialization. Study of patients with agenesis of the callosum reveals the importance of its presence in early neural development for the manifestation of the typical pattern of functional asymmetry (Chiarello, 1980); study of patients with transection of the callosum reveals its essential role in the integration of information between the two hemispheres (Sperry, 1982).

As part of an ongoing research project concerning the correlation of neuroanatomical and neuropsychological measures in human adults, postmortem measurement of the corpus callosum was made in individuals varying in hand preference, which was selected as a simple, although rough, index of hemisphere representation of language functions. It was hypothesized that if an association between callosal anatomy and hand preference were found, it would support the notion of anatomical variation as a basis for functional asymmetry. In a study of 42 brain specimens, the midsagittal area of the callosum was found to be greater in individuals with non consistent-right-hand preference (nCRH) (defined as left-hand preference on at least 1 of 12 tasks, regardless of which hand was used for writing) than in individuals with consistent-right-hand preference (CRH) (Witelson, 1985). It was suggested that the correlation of callosal size and hand preference supported the hypothesis of a correlation between callosal anatomy and functional lateralization, and that the larger callosum of the non consistent-right-handers (nCRH) might allow for greater interhemispheric communcation and thus be a basis for the greater bihemisphere representation of language functions in groups of left handers. It was further suggested that the larger callosum of nCRH may contain more fibres to support the possibly greater interhemispheric communication, and that the greater number of fibres might result from less extensive axonal elimination in nCRH than CRH during the regressive events in early neural development.

Although the total, anterior-half and posterior-half areas of the callosum were found to be larger in nCRH, the area of the posterior one-fifth region (roughly congruent with the splenium) was not different between hand groups. These results raised the issue as to whether callosal variation between CRH and nCRH is more pronounced in some regions than others. If variation in callosal morphology is associated with variation in pattern of hemisphere specialization, it might follow that those callosal regions housing fibres from cortical regions relevant to functional asymmetry would show the greatest difference between hand groups. Thus the first purpose of the present study was to subdivide the anterior and posterior halves into smaller segments which could be roughly associated with cortical regions, and to assess hand-group differences for the different callosal segments. It was predicted that nCRH would have a larger callosum than CRH particularly in those callosal segments associated with cortical regions relevant to functional asymmetry, such as the most posterior part of the body of the callosum (the isthmus) which probably includes fibres from posterior parietal and superior temporal cortical regions (in monkey, Seltzer and Pandya, 1983; Cipolloni and Pandya, 1985, respectively; in man, de Lacoste *et al.*, 1985), and the rostrum, which in the monkey appears to house fibres from inferior premotor regions (Pandya *et al.*, 1971) as well as fibres from restricted prefrontal regions (Barbas and Pandya, 1984). Less difference between hand groups was expected for callosal segments connecting cortical regions less related to functional asymmetry, such as prefrontal and occipital cortical regions, and for segments associated with hand control per se, such as central motor regions.

Callosal anatomy was also recently reported to vary with sex. In a study of 9 males and 5 females (de Lacoste-Utamsing and Holloway, 1982), it was found that the midsagittal area of the total callosum relative to brain weight tended to be larger in the female than male group and that absolute area and breadth of the splenium were greater in females. In contrast, two earlier reports on much larger samples found that the callosal area tended to be larger in males than females (Bean, 1906; Mall, 1909), as is the case for overall brain size.

In the Witelson (1985) study, no sex difference in absolute or relative size of the total callosum or splenium was observed. Following the report by de Lacoste-Utamsing and Holloway (1982), several other reports also failed to find any sex difference in total callosal or splenial size. However, in the Witelson (1985) report, a nearly significant ($P = 0.08$) interaction between hand preference and sex was found for the posterior-half area of the callosum relative to brain weight. This was not the case for the anterior half or for the splenium alone. Inspection of the interaction suggested that the degree to which the posterior half was absolutely or proportionately larger in males than females was less among CRH than in nCRH. The observation of no hand, sex, or interaction factors for the splenium itself suggested that in the remaining region of the posterior half, the posterior body, some sex difference might be present and be revealed if the posterior body were measured separately, with the factor of hand preference controlled. Thus the second purpose of this study was to examine possible sex differences in subregions of the callosum.

In the present study, the midsagittal surface of the callosum was subdivided into seven regions and direct postmortem measurements were made on a sample of 50 brains from individuals of known sex and tested hand preference. Except for the splenium, these regions have not been measured in previous studies. The specific hypotheses to be tested concerned variation in different parts of the callosum in relation to hand preference and sex. Specifically, it was predicted that nCRH would have a larger callosum than CRH in regions of the posterior body and rostrum, and that females might have a proportionately larger callosum in some region of the posterior body compared with males.

METHODS

Subject source

The subjects were cancer patients who were recruited over the past 10 years (1977–1987) to participate in a study which required taking a battery of neuropsychological tests and agreeing to a postmortem examination, with autopsy permission to be finalized by their next-of-kin at the time of death. Each subject gave informed consent for both aspects of the project, which had the approval of the institutional review board. The subjects were informed that the purpose of the project was to correlate psychological test performance with neuroanatomical measures in order to help to elucidate human brain-behaviour relationships. All subjects were aware that they had metastatic disease which was amenable only to palliative radiotherapy or chemotherapy, and that their prognosis for long-term survival was poor. The subjects were free of neurological symptoms or any debilitating symptoms when they started the project. The procedure for recruiting appropriate subjects, testing, maintaining contact with the subjects and their families until death, and requesting autopsies is complex and difficult in some aspects. A detailed report of the overall methodology is presented elsewhere (S. F. Witelson and P. B. McCulloch, unpublished results).

At the time of this report, 114 subjects had been recruited, 93 of whom had died. Autopsies were obtained for 56 of these 93 cases, and were carried out in 6 local hospitals. The sample included

16 men and 40 women. This difference is primarily due to the sex difference in the prevalence of the main types of cancer (lung and breast) which have a disease course appropriate for this project. These 56 consecutively obtained postmortems include the sample of 42 brain specimens reported on previously (Witelson, 1985).

Psychological testing

A battery of tests including standardized intelligence and memory tests, measures of various linguistic, spatial, musical and motor skills, and measures of hemisphere functional asymmetry based on hand preference and right-left perceptual tests were given to each subject. The present study concerns hand preference.

Hand preference test

A modified version of Annett's (1967) hand questionnaire was used, in which the subject was asked to demonstrate hand use, rather than to complete a questionnaire, for a series of 12 unimanual (e.g., tooth brushing) and bimanual (e.g., threading a needle) tasks. For each item, preference was recorded as right, either, or left; and scored as +1, 0, or −1, respectively. Possible scores varied from +12 to −12. Several different classification systems of hand preference are typically used in psychological studies, such as right or left-handed defined by writing hand; or right, mixed or left-handed, defined by some arbitrary criterion (e.g., right-handed as 75% right-hand preference). The classification used in this study is based on Annett's (1972, 1978) model of the classification and genetics of hand preference and included two main categories; consistent-right-hand preference (CRH) (defined as all 'right', or 'right' with some 'either' preferences), and non consistent-right-hand preference (nCRH) (defined as left-hand preference on at least one of the twelve tasks, regardless of the hand used in writing). The nCRH category included both consistent-left-hand preference (CLH) (defined as all 'left' or 'left' with some 'either' preferences), and mixed-hand preference (MH) (defined as any combination including both right and left preferences). Mixed-handers may be right-writers or left-writers. Of the 56 available brain specimens, only 54 subjects had sufficient handedness testing to allow classification. The 2 cases with limited handedness testing wrote with their right hand, but it was not determined whether they preferred their right hand on all tasks. The prevalence of CRH, MH and CLH in the sample of 54 cases was 63, 37 and 0%, which is similar to that of 66, 30 and 4% observed in large samples (Annett, 1972).

Brain removal procedure

The entire brain including the medulla was removed by the pathologist during the autopsy, according to a standard procedure designated for the project. On removal from the skull, the fresh brain was immediately weighed, and immersed in a solution of 10% neutral buffered formalin suspended by the basilar artery. The mean time interval between death and brain fixation at autopsy was 12.8 h (n = 44 cases). The other 12 brains were obtained by a different administrative route in which the subject bequeathed his body to science. This route had a different procedure. The whole body was perfused with fixative, with additional perfusion of the brain, and the brain was removed and immersed in formalin 16 days after death, in compliance with Ontario law.

Brain weights

After arrival in the laboratory, each brain obtained from autopsy was weighed again within 48–72 h after death, and then kept in a refrigerated storage room with formalin changed after 1 wk, 1 month, and thereafter ever 12 months. Brains remained in fixative in cold storage for a minimum of 3 wks before further handling. A third whole brain weight was again taken in the laboratory 3 wks after death for autopsy-obtained brains. Bequeathal-obtained brains were weighed 72 h after immersion fixation. All laboratory weights were obtained with a Sartorius balance (model 2350), accurate to 0.1 g.

Given that initial increase in brain weight after death is within the first 12 h (Appel and Appel,

1942) and that little change occurs as a result of formalin fixation (at most 5% in either direction within 28 days after death (Van Buren and Borke, 1972)), the weights at 3 wks for the autopsy-obtained brains and at 72 h after removal from the body for the bequeathal-obtained brains were chosen as roughly comparable measures. In the present study, whole brain weight was used to compare the brains of this sample with other groups. The mean brain weights for males and females in this study (mean ages were 50 and 51 yrs, respectively) were 1439 g and 1263 g, respectively ($t = 6.0$, $df = 54$, $P = < 0.0001$), similar to those reported in other studies for groups of comparable age: for example 1410 g and 1280 g in 51 to 55 yr-olds (Dekaban, 1978) or 1436 g and 1312 g for 50 to 54 yr-olds (Pakkenberg and Voigt, 1964).

Anatomical dissection and measurement

After whole brain measurements, each brain was bisected in the sagittal plane. Each hemisphere was subsequently dissected to reveal specific anatomical structures. Numerous measurements of gross anatomical features were made, including weights and volumes of the cerebral hemispheres and of parts of each hemisphere, length, breadth and area measures of the lateral and medial aspects of the hemispheres and of specific gyri or structures, and measures of the exposed superior surface of the temporal lobes (including the planum temporale) within the sylvian fossa. The size of the corpus callosum in the midsagittal plane is reported in this study.

Neuropathological evaluation of gross features was performed at each dissection stage and clinical histological examinations were undertaken when necessary. Of the 54 brain specimens having hand-preference classification, 3 had pathology related to the callosum (1 brain had cystic tumour infiltration of the posterior callosum, and 2 brains had marked pathology possibly affecting callosal anatomy), and a fourth case had some distortion created by a measurement procedure, making valid measurements of the corpus callosum in these 4 brains impossible.

Since the sexes differ significantly in brain size, a brain weight measure was used to allow comparison of the size of the callosum relative to brain size. The weight of the cerebrum, rather than whole brain weight, was selected as a possibly more precise index of extent of the cerebral cortex. After the brain was well fixed, and before the brain was bisected, the cerebellum was removed and the hindbrain cut off at the level just below the inferior colliculus. The hemispheres were then bisected, the meninges removed, and the cerebrum weight was defined as the sum of the weights of the right and left hemispheres.

Measurement of the corpus callosum

The brain was bisected by manual retraction of the hemispheres which allowed the insertion of a long brain knife to cut the callosum from front to back, with the cut passing through the septum pellucidum. The exposed medial surface of each hemisphere was then photographed with two rulers perpendicular to each other. The prints were developed at a magnification of precisely 1 : 1 for each of the rulers. In order to have a clearly visible line for the computer cursor to follow, a tracing of the callosum in each photograph was made using an x-ray viewer. All linear and area measures of the callosum were made from these tracings. Area measurements were obtained with the use of a Houston Instrument HiPad (DT11BL) having 0.125 mm resolution, in conjunction with the IBM software package, Bioquant II Digitizing Morphometry Program A5–IA2.

Seven callosal subdivisions were defined as follows. The maximal length of the callosum was taken as the line joining the most anterior and posterior points of the callosum. Perpendiculars to this axis were drawn at specific arithmetic divisions resulting in seven callosal segments. These are shown in fig. 1. The linear axis was used to divide the callosum into anterior and posterior halves; anterior, middle, and posterior thirds; and the posterior one-fifth region. The division into thirds was adopted to obtain measures comparable to previous studies. The perpendicular dropped through the anteriormost point of the inner convexity of the anterior callosum (point G in fig. 1) was used to define the most anterior segment of the callosum, region 2, roughly congruent with the genu. The line at G was also used to define the rostrum, region 1, the inferior extension of the anterior

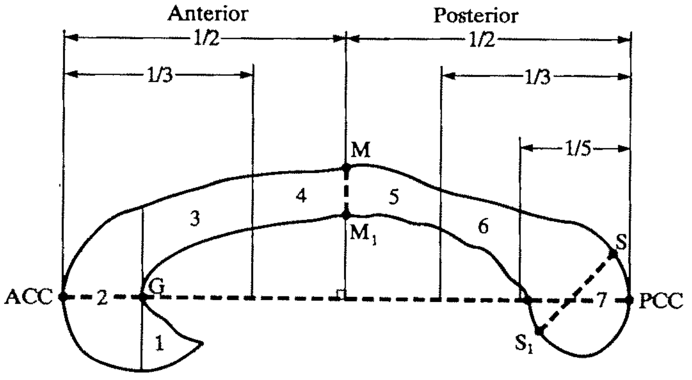

FIG. 1. Diagram of the midsagittal view of the corpus callosum of the human adult, showing the seven regional subdivisions used for area measurement, numbered 1–7. The dashed lines represent the three linear measurements. ACC and PCC indicate the anteriormost and posteriormost points of the callosum, with ACC-PCC defined as the length of the callosum; M and M_1, superior and inferior points, respectively, of the callosum at its midpoint, with MM_1 defined as the width of the midcallosum; S and S_1, superior and inferior points on the posterior bulbous region which is the splenium, chosen such that SS_1 is the length of the maximal perpendicular between two parallel lines drawn as tangents to the superior and inferior surfaces of the splenium; G, the anteriormost point on the inner convexity of the anterior callosum.

ACC-PCC was used as the linear axis to subdivide the callosum into anterior and posterior halves; anterior, middle, and posterior thirds; and the posterior one-fifth region (region 7) which is roughly congruent with the splenium. The line perpendicular to the axis at point G was used to define the anteriormost division of the callosum, roughly congruent with the genu (region 2), and the rostrum (region 1). Region 3 was defined as the anterior one-third minus regions 1 and 2. Region 4 was defined as the anterior one-half minus the anterior one-third. Region 5 was defined as the posterior one-half minus the posterior one-third. Region 6, the isthmus, was defined as the posterior one-third minus the posterior one-fifth. Regions 3, 4, 5 and 6 constitute the body of the callosum.

For easy reference in the text, the seven regions were given anatomical labels as listed below. A rough topography of callosal fibres in relation to cortical regions of origin and termination is also given, based mainly on experimental work with monkeys and on some clinical work with humans (see text for further details).

Region	*Anatomical label*	*Cortical region*
1	Rostrum	Caudal/orbital prefrontal, inferior premotor
2	Genu	Prefrontal
3	Rostral body	Premotor, supplementary motor
4	Anterior midbody	Motor
5	Posterior midbody	Somaesthetic, posterior parietal
6	Isthmus	Superior temporal, posterior parietal
7	Splenium	Occipital, inferior temporal.

portion of the callosum. Although the rostrum is treated as an extension of the genu in most studies, it was measured here as a separate region, as there are suggestions that it contains fibres from different cortical regions than does the genu. Region 3, referred to here as the rostral body, was defined as the anterior one-third region minus regions 1 and 2. Region 4, referred to as the anterior midbody, was defined as the anterior half minus the anterior one-third region. Region 5, referred to as the posterior midbody, was defined as the posterior half minus the posterior one-third region. Region 6, the isthmus, was defined as the posterior one-third minus the posterior one-fifth region. Region 7 was the posterior one-fifth region, roughly congruent with the splenium. Regions 3 to 6 constitute the body of the callosum.

These callosal regions may be associated roughly with various cortical regions, although there is considerable overlap. Possible topographic organization of callosal fibres in man is summarized in fig. 1 (legend). It is based mainly on experimental work with monkeys involving ablation/

degeneration studies (Pandya *et al.*, 1971) and the autoradiographic tracing method (for frontal regions, *see* Barbas and Pandya, 1984; for parietal regions, Seltzer and Pandya, 1983; for temporal regions, Cipolloni and Pandya, 1985; and for occipital regions, Rockland and Pandya, 1986), and also on some clinical human study (e.g., Van Valkenburg, 1913; Schaltenbrand *et al.*, 1972; de Lacoste *et al.*, 1985). The evidence is least clear for the rostrum. There is some evidence in the monkey that the rostrum contains fibres from inferior premotor as well as medial and caudal/orbital prefrontal regions (Pandya *et al.*, 1971, figs 2, 5c; Barbas and Pandya, 1984). In man, it may be that at least some fibres coursing through the rostrum come from the inferior premotor cytoarchitectonic regions, Brodmann areas 44 and 45 (D. N. Pandya, July, 1984, personal communication).

To determine the area of each region, two separate measurements were made from each photographic tracing and the mean value was calculated. The difference between these two measurements in each brain was less than 2%. For the total group of 50 brains, in the splenium for example, the mean values for the first and second measurements from the right hemisphere were 181.1 and 181.2 mm^2. The correlation between these measurements was $r = 0.999$. This procedure was used for each region in each hemisphere, and then the mean of the right and left mean values was used as the final area measure. Total callosal area was obtained by adding the final area measures of the anterior and posterior one-half regions. Again, for the total group, with splenial area as an example, the mean values for the right and left hemispheres were 181.0 and 178.2 mm^2, respectively, with $r = 0.87$ ($n = 50$, $P < 0.001$).

Three linear measures were obtained: the maximal length of the callosum as described, the width (or thickness) of the callosum at its midpoint, and the maximal breadth of the splenium. Splenial breadth was defined as the length of the perpendicular between two parallel lines drawn as tangents to the superior and inferior surfaces of the splenium. All measures were obtained in a manner similar to that described for area measures. All measurements were done blind as to sex or identity of the subject.

Sample studied

Of the total sample of 56 brain specimens, 50 cases had sufficient hand preference testing for classification and were free from pathology affecting callosal measures. All cases were Caucasian and age varied from 25 to 68 with a mean of 50.8 yrs. Table 1 presents the frequency of the different hand preference classifications for each sex. As indicated previously, there were no CLH in this sample and, accordingly, the nCRH consisted only of mixed handers (Table 1A). The nCRH included

TABLE 1. SAMPLE SIZE OF THE HAND-SEX SUBGROUPS STUDIED

A	*CRH*	*nCRH (mixed)*	*Total*
Male	9	6	15
Female	23	12	35
Total	32	18	50

B	*nCRH (mixed)*		
	Right-writer	*Left-writer*	*Total*
Male	4	2*	6
Female	8	4	12
Total	12	6	18

* One subject was a forced dextral who also performed almost all tasks with his left hand. He was classified as a nCRH left-writer. CRH = consistent-right-handers. nCRH = non consistent-right-handers.

both right-writers and left-writers as indicated in Table 1B. One-third of the nCRH wrote with their left hand.

Statistical analyses

For all statistical analyses, an α level of 5% was accepted as the level of significance and two-tailed tests were used. Several sets of data were analysed with two-way univariate analyses of variance with hand preference and sex as factors. To compare the sexes further on some of the anatomical measures with the variable of brain size controlled, two-way (hand preference and sex) analyses of covariance were performed with cerebrum weight as the covariate.

RESULTS

Comparability of hand-sex subgroups on baseline measures

Table 2 presents the descriptive statistics (mean and SD) and univariate two-factor analyses of variance (ANOVA) for cerebrum weight, age at death, and hand preference scores for the 4 hand-sex subgroups of the total sample of 50 cases. The ANOVA for age at death revealed no significant factors. The ANOVA for cerebrum weight indicated that sex was a significant factor ($P < 0.001$). Males had a larger cerebrum weight than females. Neither hand nor hand × sex were significant factors. Cerebrum weight was highly correlated with the 3-week total brain weight ($r = 0.96$, $n = 50$, $P < 0.0001$).

The mean hand-preference scores for the male and female CRH groups were similar (means = 11.2 and 11.5, respectively), each group having little variation. The mean hand-preference scores for the male and female nCRH subjects were not statistically different (mean = 2.8, min/max = -8 to $+8$, and mean = 7.0, min/max = -3 to $+10$, respectively; $t = 1.23$, df = 15, $P = 0.27$).

Hand preference and callosal size

The callosal measurements were analysed with hand preference (CRH and nCRH) and sex (male and female) treated as two factors. Table 3 presents the descriptive statistics (mean and SD) for the area and linear measurements of the callosum for each of the 4 hand-sex subgroups.

A multivariate analysis of variance (MANOVA) using the area measures of the 7 divisions of the total callosum (*see* fig. 1 and Methods) as the dependent variables, with hand preference and sex as independent factors, was carried out (BMDP 4V, 1982 revision). The MANOVA yielded a significant overall hand effect ($F = 2.49$, df = 7,40; $P = 0.03$), suggesting that the callosum was larger in nCRH than CRH. The difference between the groups was about 50 mm^2 or 7%. Neither the overall sex factor ($F = 2.13$; df = 7,40; $P = 0.06$) nor the hand × sex interaction ($F = 1.99$; df = 7,40; $P = 0.08$) was significant.

The univariate two-factor analyses of variance for the area measure for each callosal region revealed a pattern of regional differences for each group (hand and sex) factor. The results of the univariate ANOVAs are presented in Table 3.

TABLE 2. MEANS AND SDs FOR BASELINE MEASURES OF AGE, CEREBRUM WEIGHT AND MAGNITUDE OF HAND PREFERENCE FOR THE FOUR HAND-SEX SUBGROUPS AND THE RESULTS OF UNIVARIATE ANALYSES OF VARIANCE

	Male				*Female*				*Univariate ANOVA*[a]					
	CRH ($n = 9$)		*nCRH* ($n = 6$)		*CRH* ($n = 23$)		*nCRH* ($n = 12$)		*Hand* (H)		*Sex* (S)		$H \times S$	
Measure	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F*	*P*	*F*	*P*	*F*	*P*
Cerebrum weight (g)	1174	64	1241	103	1047	69	1022	85	0.03	0.87	47.30	0·00*	3.64	0.06
Age at death (yrs)	49.6	12.3	50.5	11.4	50.8	8.4	52.0	8.7	0.16	0.69	0.20	0.66	0.00	0.97
Hand preference score[b]	11.2	1.0	2.8	7.7	11.5	1.3	7.0	4.4	[c]					

[a] SPSS ANOVA, classical experimental approach. [b] Hand preference score is based on the 12-items of Annett's (1967) hand preference questionnaire and may vary from +12 to −12, which reflects 100% right and left preference, respectively. [c] Comparison of mean hand preference scores of the two nCRH groups: t = 1.23, df = 15, $P = 0.27$. The nCRH female group was based on only 11 cases as 1 subject did not have sufficient handedness testing to obtain a score. * $P < 0.001$. CRH = consistent-right-handers; nCRH = non consistent-right-handers.

TABLE 3. MEANS AND SDs FOR MEASUREMENTS OF THE CORPUS CALLOSUM FOR THE FOUR HAND-SEX SUBGROUPS AND THE RESULTS OF UNIVARIATE ANALYSES OF VARIANCE

		Male				*Female*				*Univariate ANOVA*[a]					
		CRH (*n* = *9*)		*nCRH* (*n* = *6*)		*CRH* (*n* = *23*)		*nCRH* (*n* = *12*)		*Hand* (*H*)		*Sex* (*S*)		*H* × *S*	
Callosal region		*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F*	*P*	*F*	*P*	*F*	*P*
Area measures (mm^2)															
Anterior half		368.7	42.3	415.5	46.1	343.3	42.6	353.0	58.2	2.36	0.13	7.41	0.01	1.53	0.22
Rostrum	(1)[b]	23.8	11.8	33.0	7.7	23.4	8.7	22.7	9.3	2.00	0.16	3.22	0.08	2.80	0.10
Genu	(2)	170.5	27.3	186.5	21.5	149.1	17.9	160.0	38.8	2.57	0.12	8.19	0.01	0.10	0.76
Rostral body	(3)	88.5	23.6	101.2	18.5	87.1	20.1	92.4	15.7	2.07	0.16	0.68	0.41	0.35	0.56
Anterior midbody	(4)	86.0	9.0	94.9	16.2	83.6	14.1	78.0	10.4	0.16	0.69	5.56	0.02	3.21	0.08
Posterior half		305.7	23.2	370.8	69.3	308.2	43.3	315.5	43.3	3.77	0.06	2.05	0.16	4.20	0.05
Posterior midbody	(5)	70.6	5.7	87.1	21.3	71.1	10.4	73.7	7.0	7.65	0.01	3.46	0.07	4.06	0.05
Isthmus	(6)	54.0	10.7	84.3	27.3	64.5	12.0	66.4	10.8	13.07	0.00*	0.69	0.41	10.07	0.00*
Splenium	(7)	181.2	15.5	199.3	29.2	172.3	28.4	175.3	31.8	1.46	0.23	3.51	0.07	0.74	0.39
Total callosum		674.5	44.1	786.3	111.6	650.4	79.8	668.4	89.7	3.88	0.05	5.64	0.02	3.30	0.08
Linear measures (mm)															
Callosal length		71.6	3.0	76.2	7.2	71.0	5.1	71.8	2.2	2.28	0.14	2.14	0.15	1.64	0.21
Midcallosal width		6.9	0.9	7.2	1.7	6.5	0.8	6.3	0.5	0.01	0.92	4.71	0.04	0.82	0.37
Splenial maximal breadth		14.4	2.4	12.1	0.9	12.8	2.8	12.5	1.8	1.78	0.19	1.33	0.26	1.88	0.18

[a] Univariate ANOVA for the seven callosal regions are based on univariate ANOVA from BMDP 4V MANOVA, Rev. 1982; [b] Numbers refer to the callosal regions as indicated in fig. 1. * $P < 0.001$. CRH = consistent-right-handers; nCRH = non consistent-right-handers.

Hand preference and callosal regions

The results of the ANOVA indicated that the area measures of only two regions, the isthmus (region 6) and the adjacent posterior midbody (region 5), showed a significant hand factor. These results indicate that these two regions were responsible for most of the overall difference between hand groups. Together they compose the posterior body of the callosum. The area of the isthmus was larger in the nCRH than CRH by 18%, and in the posterior midbody by 10%.

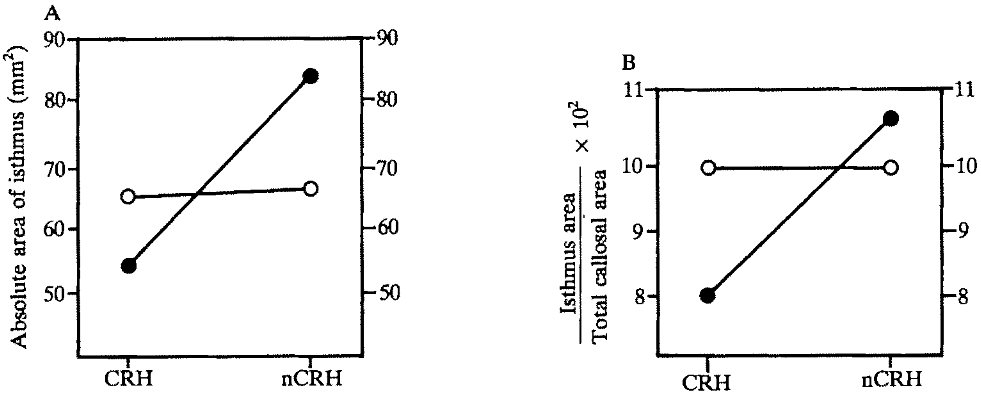

FIG. 2. Mean area for the isthmus for (A) absolute size and (B) size relative to the total callosum for the four hand-sex subgroups. CRH = consistent-right-handers; nCRH = non consistent-right-handers. Individual comparisons indicated that in (A) the two male hand groups differed ($P < 0.05$), and the male and female CRH groups tended to differ ($P < 0.07$); and in (B) the two male groups differed ($P < 0.01$), and the male and female CRH groups differed ($P < 0.01$). Filled circles (male); open circles (female).

For both regions 5 and 6, the hand × sex interaction was significant. Subsequent multiple comparisons using the Student-Newman-Keuls procedure indicated that in each case, there was a significant difference between hand groups for males, but not for females. In each case, the values of the two female subgroups were between those of the two male groups. For males, the difference in isthmus area between the two hand subgroups was 56%, as may be calculated from Table 3 and shown graphically in fig. 2A. There was little overlap between the two male subgroups: only 2 males of the nCRH group fell within the distribution of the CRH group. For the posterior midbody, the difference between the two male subgroups was 24%, and the separation of the distibution of scores was similar to that for the isthmus.

Fig. 3 presents a sketch of the callosum of each of the brains in the CRH and nCRH male subgroups, showing the more common anatomy of a depression on the superior surface of the isthmus and associated thinner area in this region in the CRH compared with the nCRH males.

The area measures of the four anterior regions and of the splenium showed no significant hand or hand × sex effects (*see* Table 3), nor did any of the three linear

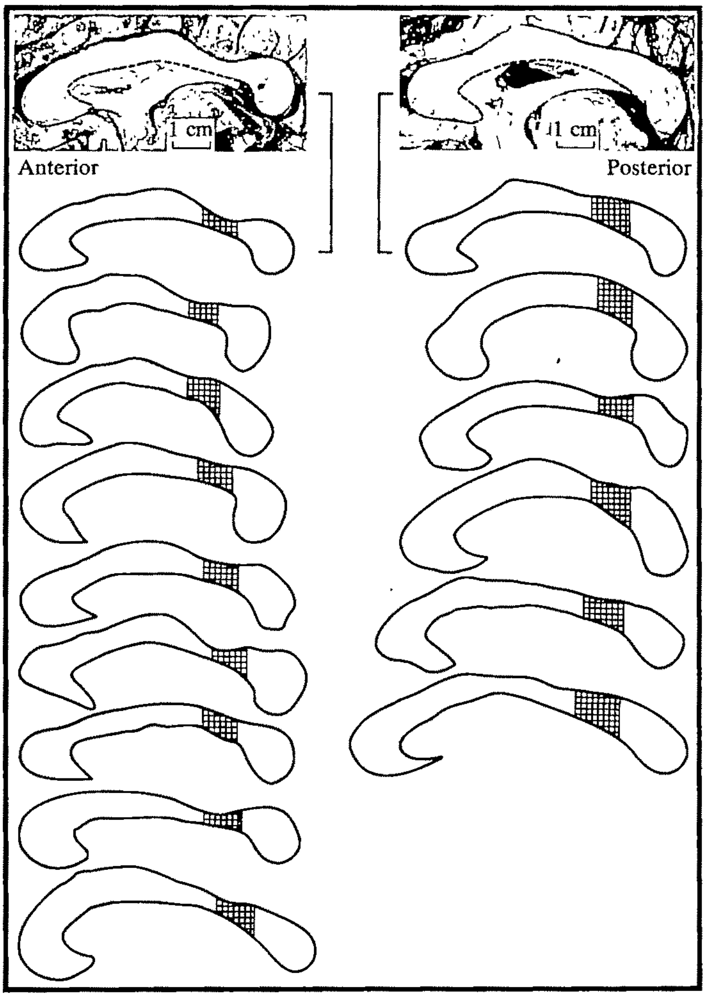

FIG. 3. Tracings of the total callosum in the midsagittal plane for each of the 9 CRH males, shown on the *left* side; and for each of the 6 nCRH males, shown on the *right* side. For each group, a photograph of the first specimen is presented together with its tracing. The boundary of the callosum in the photographs is indicated by dashed lines. The isthmus (region 6) is indicated by a grid region on each tracing. Note the greater frequency of a depression in the superior border of the isthmus and a thinner isthmus region in the brains of CRH than nCRH. Four of the 6 nCRH have a larger isthmus than any of the CRH; with the factor of age controlled, 5 of the 6 nCRH have a larger isthmus.

measures. Although only regions 5 and 6 showed a significantly greater area for nCRH than CRH males, the mean area values tended to be larger for nCRH for each of the seven callosal regions. For the rostrum (region 1), the difference was 39%. In contrast, for the female hand subgroups, with at least double the sample size of the male groups, the mean values of the nCRH group tended to be larger for most regions, but only minimally.

Hand preference and callosal area with age controlled

In males, total callosal area correlated with chronological age ($r = -0.55$, $n = 15$, $P = 0.04$). A fuller description of the relationship between callosal size and age follows in a later section. The difference in callosal size between the two male hand groups was even clearer with the factor of age controlled. A discriminant function analysis for males using age at death and total callosal area as predictors of membership in the hand group (CRH versus nCRH), yielded a value for Wilks' Lambda of 0.436, $\chi^2 = 9.94$, $df = 2$, $P = 0.01$. Only one nCRH subject was misclassified, resulting in correct classification of 93% of the cases.

The equation from the discriminant function analysis that predicted hand group classification was:

$$H = 9 \text{ age (yrs)} + 1.5 \text{ callosal area (mm}^2) - 1563 \qquad \text{(Equation 1)}$$

For the 93% correctly classified cases, the maximum discriminant function score of the CRH group was 22 and the minimum score of the nCRH group was 96. A middle cut-off point of 60 was selected, with a value of H less than 60 indicating a CRH, and a value of H greater than 60 indicating a nCRH.

The brains of 2 male subjects were obtained subsequent to the sample of 50 cases on which the present analyses are based. One case was a 59-yr-old man, with a total callosal area of 677.3 mm^2. Using Equation 1, the value of H obtained was -19, which classified him as a CRH. The psychological test results confirmed that he was a CRH. The other case was a 66 yr-old man with a total callosal area of 702 mm^2, resulting in a value for H of 84, which classified him as a nCRH. He was nCRH (a right-writer).

Sex and callosal size

Sex and absolute size of callosal regions

The overall sex factor in the MANOVA did not reach significance, although the male group tended to have a larger callosum. However, the univariate two-factor ANOVA for total callosal area indicated a larger callosum in males than females ($P = 0.02$, Table 3). The univariate ANOVAs for the callosal regions indicated that the sexes differed in some regions (Table 3). Males had larger areas in two anterior regions, the genu (region 2) and the anterior midbody (region 4). The hand and hand × sex effects for these regions were not significant. The sex factor did not reach significance for the splenium, although males tended to have the larger value ($P = 0.07$). For each of these three regions, the mean scores for each of the two male groups were greater than the scores for the two female groups.

In contrast, the other four callosal regions (regions 1, 3, 5 and 6) showed no main effect of sex and, unlike the above measures, were not smaller in females. There was, as indicated previously, a hand × sex interaction for each of the two posterior body regions (regions 5 and 6), which indicated that the two hand groups

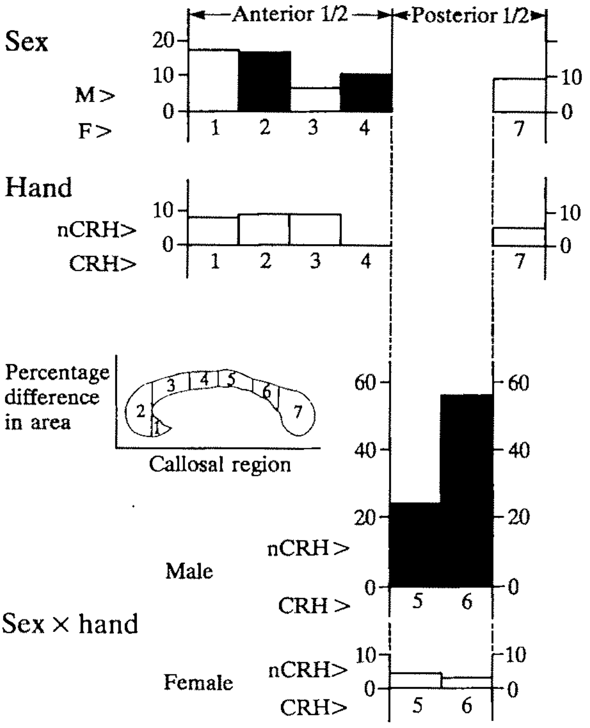

FIG. 4. Schematic summary of the percentage difference in absolute area for each of the seven callosal regions for each of the factors, sex, hand preference, and sex × hand. The closed bars indicate statistically significant differences; the open bars represent differences not significant at $\alpha = 0.05$. The numbers 1-7 on the x axes refer to the number of the callosal region as indicated in fig. 1 and repeated in the insert of the callosal sketch in this figure. The y axes represent the percentage difference in area between the two groups under comparison, with greater scores for males or nCRH represented above the x axes. CRH = consistent-right-handers; nCRH = non consistent-right-handers; M = male; F = female. Note that the significant sex differences occurred in anterior regions. The significant handednes differences occurred in posterior regions, but with a sex × hand interaction. The significant interaction effect for the isthmus is presented in more detail in fig. 2.

differed in males, but not in females. In addition, for the isthmus, female CRH tended to have a larger area than male CRH ($t = 1.9$, df = 46, $P = 0.07$; fig. 2A).

The ANOVAs for linear measurements indicated no sex difference for callosal length or maximal breadth of the splenium. Midcallosal width, which borders the anterior midbody which was larger in males, was also found to be larger in males (Table 3).

Fig. 4 presents a schematic summary of the percentage difference in absolute area for the seven callosal regions for the factors of hand preference and sex.

Sex and area of callosal regions relative to total callosum

In one region, the isthmus, the absolute area tended to be larger in female than male CRH. Since males had a larger total callosum than females (*see* Table 3), to examine further a possible sex difference in the isthmus, the ratio of the isthmus area to total callosal area was analysed with a two-factor (hand and sex) ANOVA. A similar analysis was performed for the ratio of the splenium (the posterior one-fifth) to total callosal area, for comparison with previous reports which used this ratio. The ratios and results of their analyses are given in Table 4.

For the relative isthmus area, the main factor of sex became significant. Females had a proportionately larger isthmus. Hand remained a significant factor, as was the case for absolute isthmus area, with nCRH having a larger ratio. The hand × sex term also remained significant, and multiple comparisons with the Student-Newman-Keuls procedure revealed that the hand groups differed in males, but not in females. Additionally, female CRH had a larger relative isthmus than male CRH ($t = 3.34$, $df = 46$, $P = 0.01$). These results are presented in Table 4 and also graphically in fig. 2B. The ANOVA for relative splenial area indicated no significant factors.

Sex and callosal size relative to cerebrum weight

The two sex groups in the present sample differed in brain weight as is the case in the general population (*see* Methods) and also in cerebrum weight (Table 2). Possible sex differences in callosal size relative to brain size were examined with the factor of cerebrum weight controlled in analyses of covariance (ANCOVA). The correlations of callosal area measures with cerebrum weight are presented first.

Correlation of callosal areas with cerebrum weight

Table 5 presents the Pearson product-moment correlations of cerebrum weight with total and regional callosal areas for the total group and for each sex separately. Total callosal area correlated significantly with cerebrum weight for the total group ($r = 0.48$, $n = 50$, $P = 0.0002$). For males the correlation was $r = 0.49$ ($n = 15$, $P = 0.06$); for females, $r = 0.32$ ($n = 35$, $P = 0.06$).

For the total group, the area of each callosal region correlated significantly with cerebrum weight except for the isthmus ($r = 0.18$, $n = 50$, $P = 0.22$) and the posterior midbody ($r = 0.20$, $n = 50$, $P = 0.18$), the two regions most strongly associated with the factor of hand preference. In general, each sex group showed similar correlations to those of the total group, but they did not reach statistical significance. This may be a power issue due to smaller sample size.

Sex and regional area relative to cerebrum weight

Two-factor (hand and sex) ANCOVAs, with cerebrum weight as the covariate, revealed that cerebrum weight was a significant covariate for each region, except for the isthmus ($P = 0.17$) and for the posterior midbody ($P = 0.10$), similar to the results of the product-moment correlations.

No main sex effect was observed for any measure. For the three callosal measures which showed sex differences in absolute size, total area, genu and anterior midbody, significant main sex effects were not obtained when cerebrum

TABLE 4. MEANS AND SDs FOR RELATIVE AREAS OF THE ISTHMUS AND SPLENIUM FOR THE FOUR HAND-SEX SUBGROUPS AND THE RESULTS OF ANALYSES OF VARIANCE

	Male				*Female*				*Univariate ANOVA*[a]					
	CRH ($n = 9$)		*nCRH* ($n = 6$)		*CRH* ($n = 23$)		*nCRH* ($n = 12$)		*Hand* (H)		*Sex* (S)		$H \times S$	
Ratio score	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*F*	*P*	*F*	*P*	*F*	*P*
Isthmus/total callosum	0.080	0.02	0.106	0.02	0.099	0.01	0.099	0.01	4.31	0.04	4.92	0.03	8.60	0.01
Splenium/total callosum	0.269	0.02	0.253	0.01	0.265	0.02	0.262	0.03	0.51	0.48	0.01	0.93	0.93	0.34

[a] SPSS ANOVA, classical experimental approach. CRH = consistent-right-handers; nCRH = non consistent-right-handers.

TABLE 5. PEARSON PRODUCT-MOMENT CORRELATIONS OF CEREBRUM WEIGHT WITH TOTAL AND REGIONAL CALLOSAL AREAS

	Total ($n = 50$)		*Male* ($n = 15$)		*Female* ($n = 35$)	
Variable	*r*	*P*	*r*	*P*	*r*	*P*
Cerebrum weight with						
Total callosum	0.48	< 0.001	0.49	0.06	0.32	0.06
Rostrum (1)[a]	0.30	0.04	0.30	0.28	0.18	0.30
Genu (2)	0.54	< 0.001	0.49	0.06	0.36	0.04
Rostral body (3)	0.26	0.06	0.22	0.44	0.28	0.10
Anterior midbody (4)	0.35	0.01	0.43	0.10	0.14	0.44
Posterior midbody (5)	0.20	0.18	0.20	0.48	−0.02	0.92
Isthmus (6)	0.18	0.22	0.24	0.38	0.22	0.20
Splenium (7)	0.37	0.01	0.47	0.08	0.21	0.22

[a] Numbers refer to the callosal regions as indicated in fig. 1.

weight was controlled [F (4, 45) = 0.20, $P = 0.66$; F = 0.05, $P = 0.83$; F = 0.00, $P = 0.99$, respectively]. Sex × hand effects were not significant. For the remaining five callosal regions which did not show overall sex differences in absolute size, no main sex effect or any new sex × hand interaction emerged in the ANCOVAs. For all regions, hand remained a significant factor in the ANCOVAs, as in the ANOVAs presented in Table 3.

The correlation of isthmus size with cerebrum weight was low and nonsignificant. Further inspection revealed that for the total CRH group, there was a low correlation ($r = -0.16$, $n = 32$, $P = 0.38$), but for the total nCRH group, the correlation appeared greater ($r = 0.42$, $n = 18$, $P = 0.08$). A z-test was performed to compare the two correlation coefficients ($z = 1.92$, $P = 0.06$). A more stringent test of a difference between hand groups for correlation of isthmus area with cerebrum weight was done using a two-factor ANCOVA, with cerebrum weight and cerebrum weight × hand as two covariates. The latter covariate was significant ($P = 0.009$), indicating that the covariate of cerebrum weight interacted with the main factor of hand preference and therefore, that the correlation of isthmus size with cerebrum weight was different in the two hand groups.

The results of this analysis also indicated that the overall ANCOVA of isthmus size with cerebrum weight as the covariate was not appropriate. Accordingly, two one-factor (sex) ANCOVAs, one for each hand group with cerebrum weight as the covariate, were done. For the nCRH, sex was not a significant factor [covariate: $P = 0.09$; F (2, 15) = 0.78, $P = 0.39$]. For the CRH, sex was a significant factor [covariate: $P = 0.35$; F (2, 29) = 4.79, $P = 0.04$). CRH females had a larger isthmus relative to cerebrum weight than CRH males (adjusted means were 65.3 and 51.9 mm^2, respectively, a difference of 26%). These results are similar to the sex difference observed for isthmus area proportional to total callosal area in CRH (*see* fig. 2B).

Correlation of callosal size and chronological age

The four hand-sex subgroups did not differ in means score or SD for age at death. The mean age for each subgroup was approximately 50 yrs (*see* Table 2), but age varied. Minimum and maximum ages of the total group were 25 and 68 yrs. Table 6 gives the Pearson product-moment correlations of age with total callosal area for each hand-sex subgroup and for the combined sex groups.

Sex difference in the correlation of callosal area and age

The total male group and each male subgroup showed a large and significant negative correlation of total callosal area with age (*see* Table 6). In contrast, the correlations of callosal size with age for the three female groups were close to zero. A two-factor (hand and sex) ANCOVA for callosal size with age and age × sex as two covariates revealed that both were significant covariates ($P =$ 0.03 and 0.05, respectively), and that the factor of age interacted with the factor

TABLE 6. PEARSON PRODUCT-MOMENT CORRELATIONS OF AGE WITH TOTAL CALLOSAL AREA FOR THE FOUR HAND-SEX SUBGROUPS AND THE TOTAL GROUP

	Male						*Female*						*Total (n = 50)*	
	CRH (n = 9)		*nCRH (n = 6)*		*Total (n = 15)*		*CRH (n = 23)*		*nCRH (n = 12)*		*Total (n = 35)*			
Variable	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age with total callosal area	−0.73	0.02	−0.86	0.02	−0.55	0.04	−0.11	0.60	0.05	0.88	−0.05	0.80	−0.25	0.08

TABLE 7. MEAN AREA MEASUREMENTS OF TOTAL AND POSTERIOR BODY REGIONS OF THE CALLOSUM FOR THE nCRH SUBGROUPS BASED ON WRITING HAND

			Callosal region (mm^2)		
		Hand score	*Total callosum*	*Posterior midbody*	*Isthmus*
Group	*n*	*Mean*	*Mean*	*Mean*	*Mean*
Male					
CRH	9	11.2	674.5	70.6	54.0
nCRH					
Right-writer	4	7·8	778.6	89.4	80.2
Left-writer	2[a]	−7.0	801.6	82.7	92.5
Female					
CRH	23	11.5	650.4	71.1	64.5
nCRH					
Right-writer	8	9.3	655.8	75.6	65.2
Left-writer	4	1.0[b]	693.7	69.9	68.8

[a] One subject was a forced dextral for writing. [b] Mean hand score is based on n = 3, as full handedness testing was not available for one subject. CRH = consistent-right-handers; nCRH = non consistent-right-handers.

of sex. This result indicates that callosal size and age covary differently in the sexes.

CRH-nCRH classification versus writing-hand classification

The most frequently used classification of hand preference is based on the hand preferred in writing, not the CRH-nCRH dichotomy used in the present study. The nCRH group included 12 subjects who wrote with their right hand (nCRH right-writers) and 6 who wrote with their left hand (nCRH left-writers) (*see* Table 1 and Methods). The mean callosal areas for those regions found to differentiate between CRH and nCRH are given in Table 7 for the CRH group and two nCRH subgroups based on writing-hand for each sex separately. These scores allow comparison between (1) CRH (all of whom write with their right hand) versus nCRH right-writers, and (2) all right-writers (CRH plus nCRH right-writers) versus left-writers. The subgroups are small and few statistical analyses were possible. However, visual inspection of the means and some analyses revealed a pattern.

Writing hand does not appear to be the main differentiating factor in callosal size. For males, t tests showed that even nCRH right-writers had larger total callosal and isthmus areas than CRH ($t = 2.3$, $df = 11$, $P = 0.04$, for each region). In contrast, the scores for the nCRH right-writers and nCRH left-writers were more similar on each of the three callosal measures. The difference between the more traditional 'right-handed' group (CRH combined with nCRH right-writers) and 'left-handed' group (left-writers) was attenuated compared with the difference between CRH and nCRH. For females the scores for all three hand subgroups were similar, as was the case for CRH versus total nCRH comparisons previously. The difference between the two female nCRH writing groups in total callosal area was not significant ($t = 0.67$, $df = 10$, $P = 0.5$). Inspection of the mean values presented in Table 7 suggested that nCRH right-writers, whether male or female, tended to have smaller total and isthmus areas than nCRH left-writers who were more left-biased.

The correlation of magnitude of hand preference with callosal size was examined. Since most CRH had a score of $+12$, no correlational analyses were possible for the CRH group. Analyses were possible for nCRH. Since hand preference was a factor in callosal anatomy in males, but not in females, each sex was analysed separately. For nCRH males ($n = 6$), the Pearson product-moment correlation for hand-preference score with total callosal area was $r = -0.10$; with posterior midbody area was $r = 0.16$; and with isthmus area was $r = -0.21$, all low and statistically nonsignificant. The correlation for isthmus size with cerebrum weight and age partialed out was $r = -0.75$ ($P = 0.25$). For nCRH females ($n = 11$), the zero-order correlations were 0.06, 0.22 and 0.09, respectively, all nonsignificant.

None of the 50 subjects was CLH (Table 1), which prevented examination of the factor of consistency of hand preference (regardless of direction) versus nonconsistency or mixed preference. One male subject, a forced dextral, showed near CLH preference. Aside from writing, he preferred his right hand on only

1 of the 12 tasks (use of scissors). This subject, age 60 yrs, had scores of 721.1, 77.0 and 76.5 mm^2 for the total callosum, isthmus and posterior midbody, respectively. In comparison, the oldest CRH male, age 59 yrs, had smaller scores of 617.4, 46.3 and 74.6 mm^2, respectively.

DISCUSSION

In a sample of 50 human brains, direct measurement of the midsagittal area of the human corpus callosum showed considerable variation in overall area, from 450 to 906 mm^2. These values are very similar to the minimum and maximum values observed in other studies of postmortem measurement of callosal anatomy, such as 368 and 913 mm^2 in an older study of 117 cases (Bean, 1906), 428 and 936 mm^2 in a sample of 50 cases (Malobabic *et al.*, 1985), and 439 to 905 mm^2 in a sample of 22 cases (Demeter *et al.*, 1988). In the present study, variation in callosal morphology was found to be associated with the factors of hand preference, sex, brain weight and chronological age.

Callosal morphology and hand preference

Midsagittal area of the total callosum was found to be larger in a group of 15 nCRH than a group of 35 CRH, including both sexes, as reported previously for a smaller sample (Witelson, 1985). In the present study, the callosum was partitioned into seven regions, roughly approximating the topography of callosal fibres in relation to their cortical fields of origin and termination. Each callosal subregion at least tended to be larger in nCRH than CRH, but the hand groups did not differ significantly in size of the anterior body segments, the genu, or the splenium. The hand groups did differ in the two segments (posterior midbody and isthmus) of the posterior body, the region defined between the midpoint of the callosum and the splenium. These results are consistent with the prediction that if callosal anatomy is related to hemisphere specialization, then certain parts of the callosum, including the posterior body, may be particularly associated with hand preference.

The finding of an association between size of the posterior callosal body and hand preference adds to a growing body of data involving more than a dozen studies in which hand preference and other indices of hemisphere specialization have been related to gross anatomical features, most reliably, right-left asymmetry in sylvian fissure and occipital lobe measures (reviewed in Witelson, 1980; Witelson and Kigar, 1988*a*).

Study of the posterior body regions was guided by suggestions of earlier results (Witelson, 1985, 1986) and also by neuropsychological considerations of lateralization of function. However, prior knowledge of 2 newly found papers on the morphology of the human callosum, which have not been cited by other recent reports on callosal anatomy, might have served to pinpoint the posterior body as the region to examine for individual differences. A detailed study of the morphology of the callosum in 50 brains carried out in Yugoslavia (Malobabic *et al.*, 1985) reported that the thinnest part of the callosum occurs in the posterior body—in the region defined as the isthmus in the present paper. The Malobabic study reported that this thinning of the callosum has considerable variability and is highly successful in predicting the variability of the total midsagittal area of the callosum. A similar observation was reported in an older study at the Montreal Neurological Institute concerning the effects of variation in midsagittal anatomy on the encephalogram and cerebral angiogram (McRae and Castorina, 1963). It was reported that the large variation in callosal anatomy was due to the frequent presence of the depression on the superior surface of the posterior part of the body of the callosum. The isthmus region was also found to be a key region in individual differences in the present study (as illustrated in fig. 3). The regions of the posterior midbody and isthmus were not measured separately in other recent studies of the human callosum except in a study by Oppenheim *et al.* (1987) which measured a somewhat similarly defined region, but did not have any measures of hand preference.

There was a suggestion in the earlier report (Witelson, 1985) that callosal size was associated with hand preference in interaction with sex. The present study of subregions revealed a clear hand × sex interaction for each of the two posterior body regions and thus further clarified the factor of hand preference in callosal size. For both segments, the hand groups differed in males, but not in females. In other words, the association of callosal size with hand preference occurred mainly in males; in contrast, in females, callosal size appeared unrelated to hand preference. For males only, the isthmus was larger by 56%, and the posterior midbody by 24%, in nCRH than in CRH.

The association of hand preference and callosal anatomy in males was even stronger with chronological age controlled. Total callosal area showed a high and significant negative correlation with advancing age in males. With age controlled, there was no overlap in scores for callosal area between the two male hand groups, except for 1 case. In 2 cases (1 CRH, 1 nCRH) acquired after the analyses of this study, hand classification was correctly predicted on the basis of total callosal area and age. Such results further support the association between hand preference and callosal size in males. There was a wide separation between the sets of scores of the two male subgroups, consistent with a dichotomy in callosal anatomy between CRH and nCRH males. This finding is consistent with the dichotomous model of Annett (1972, 1978) for the genetics of hand preference and language lateralization, which postulates that there are two groups of individuals, those having the 'right-shift' allele (RS^+) either in the homozygous or heterozygous condition, and those without the gene (RS^-).

The group of nCRH included both right-writers and left-writers. NonCRH right-writers (mixed right-handers) are usually strongly right-handed, just not consistently so. Even the group of male nCRH right-writers (mean hand score = 7.8) had a significantly greater callosum than male CRH (mean hand score = 11.2). In contrast, the nCRH right-writers did not differ from the remaining nCRH (left-writers), who were strongly left-handed (mean score = −7.0). The hand difference in callosal anatomy was obscured when left-writers were compared to the combined group of CRH and mixed right-handers. Such results suggest that writing hand per se is not a main factor related to callosal size.

This issue is relevant to 2 recent reports of callosal size and handedness, both of which classified handedness groups on the basis of writing hand. Both studies used magnetic resonance (MR) imaging to measure callosal size. In one report, hand preference was based on a five-item test of well-practised items (Kertesz *et al.*, 1987). No difference in callosal area was found between 'right-handers' and 'left-handers' for either sex. The group of 'right-handers' was defined to include nCRH (even the 'strong right-handers' could score as low as 0.5 out of 1.0 on the hand-preference scale). On the basis of population frequencies (Annett, 1972), nCRH right-writers could consititute as much as 22% of 'right-handers'. In the present study, a similar analysis of all right-writers versus left-writers also yielded no difference in callosal area. The second MR report involved male control groups of different hand preference in a study of schizophrenics (Nasrallah *et al.*, 1986). Again no difference in callosal size was found between hand groups. The definition of hand classification was not given and again 'right-handers' probably included nCRH right-writers. Two similar studies in abstract form only have also been reported, using MR scans and hand preference based on writing hand. Yoshii *et al.* (1986) reported no difference in callosal size between a group of 5 left-handers and 28 right-handers. Harris *et al.* (1987) reported a trend towards greater callosal area in left-handers.

These MR studies are not comparable to the present study in the measure of hand classification used, which may contribute to the inconsistent results. In addition, anatomical measurement was very different. Study of the concordance between direct postmortem and MR measurement of callosal size remains to be done. In the two complete MR reports, no minimum and maximum values of callosal area were given, nor were SDs given in the Kertesz *et al.* (1987) report, which limits comparison between the different types of measures. These early MR studies involved scans of limited resolution which was accentuated by magnification to life-size projected images for planimetric measurement. They also used scan slices as thick as 10 mm which necessarily yield area measures which reflect the maximal area outline over the breadth of the slice. Such scans may not be sufficiently precise technically for the order of individual differences in callosal size. It is also possible that other, as yet unknown, factors contribute to the inconsistent results between studies.

In the present study of 50 brains, no cases of CLH were available, nor were any presented separately in the MR studies. CLH constitute only about 4% of the population. MR scans were obtained on two CLH male volunteers (Witelson, 1985). The results suggested that callosal area in these cases was greater than the postmortem measures for the CRH males, but similar to the nCRH. Such information is relevant to the issue of whether it is the direction of hand preference, or merely consistency (regardless of direction) versus nonconsistency of hand preference that is associated with callosal size. However, these results can only be considered as very tentative, as comparison between postmortem and MR measurement is questionable, especially as the MR scans used might be expected to yield larger values than those obtained from true two-dimensional surfaces.

The correlation of magnitude of hand preference and callosal anatomy was examined in nCRH males. In nCRH males, callosal anatomy varied with both cerebrum weight and age. With these two factors controlled, the correlation of isthmus area with hand score in nCRH males was high ($r = -0.75$), but not statistically significant. Since sample size was very small ($n = 6$), and the lack of significance could be due to insufficient power, a larger sample would need to be studied before a lack of correlation is accepted. Such a correlation, if reliable, would suggest that among mixed handers, the greater the degree of left handedness, the greater callosal size. Since hand preference score hardly varies among CRH by definition, examination of this issue in CRH would require measures of manual skill or performance which do vary among CRH. Although there may be a dichotomy in callosal size between CRH and nCRH, it remains to be determined whether magnitude of asymmetry in hand preference is correlated with callosal size.

Callosal anatomy and hemisphere specialization

Since hand preference is associated with the pattern of hemisphere specialization (Bryden, 1982), the association of handedness with callosal size suggests that variation in callosal anatomy may be associated with hemisphere specialization. If callosal morphology is part of a basis of hemisphere specialization, then those callosal segments housing fibres from cortical regions related to functional asymmetry might show the greatest difference between hand groups. It was suggested that the posterior midbody of the callosum likely includes fibres from somaesthetic and posterior parietal regions, based mainly on evidence from rhesus monkey (Pandya *et al.*, 1971; Seltzer and Pandya, 1983). Posterior parietal regions involve asymmetric representation of some spatial perceptual functions (de Renzi, 1982). The isthmus has been shown in monkey (Cipolloni and Pandya, 1985) and man (de Lacoste *et al.*, 1985) to house fibres from posterior superior temporal as well as posterior parietal regions, which might include the gyri situated at the temporoparietal junction. Accordingly, the isthmus would be likely to be associated with the posterior language region of the cortex.

As predicted, it was found that the callosal regions which showed the greatest difference between CRH and nCRH were the posterior body segments, which supports the hypothesis that variation in callosal morphology may be part of a biological basis of hemisphere specialization. The uniqueness of this result is highlighted by the lack of difference between hand groups in size of the genu, which connects prefrontal regions (Barbas and Pandya, 1984) or the splenium, which connects occipital and inferior temporal regions (Pandya and Seltzer, 1986; Rockland and Pandya, 1986), cortical region less involved in functional asymmetry. Hand-group differences were also not observed for anterior body segments, suggesting that the motor aspects per se of hand preference may not be related to callosal morphology.

The hand-group differences in the posterior body were found only in males. The lack of association between callosal anatomy and handedness in females was not expected. This result, like neuropsychological data of sex differences (Kimura, 1987), points to sex differences in aspects of lateralization, to be discussed in the next section.

It was also suggested that the hand groups might differ in size of the rostrum. In monkey, only medial and caudal/orbital prefrontal cortex was observed to send fibres through the rostrum (Barbas and Pandya, 1984); inferior premotor regions appeared spared after sectioning of the rostrum (Pandya *et al.*, 1971). Such results suggest that in man, the inferior premotor region, which would include Broca's area, might send fibres through the rostrum (Pandya, 1984). The rostrum was found to be 39% larger in nCRH than CRH males. Although this difference is not statistically significant, the size of the difference, if reliable, may be biologically significant. The variability of rostrum area was large compared to other regions. This factor, combined with the small sample size, may result in insufficient power. The observed difference of 9.2 mm^2 between the two hand groups, and the pooled SD of 10.4 would be statistically detected with larger samples of 17 cases per group (α level of 5% and 70% power). The clearer difference between hand groups for the posterior body than the rostrum parallels the clearer right-left asymmetry found for the planum temporale than for frontal speech areas. No reliable asymmetry has been demonstrated in the five available studies of the frontal operculum (reviewed in Witelson and Kigar, 1988*a*).

Left handers as a group have a greater prevalence and a greater degree of bihemispheric representation of language and spatial perceptual skills than do right handers. In Amytal studies of speech lateralization, bilateral speech representation is reflected by speech interruption with injection to either hemisphere, not by a lack of speech interruption on both sides (Milner, 1974, p. 84). This situation suggests that bilateral speech representation involves an integrated or shared unit across the two hemispheres, rather than two independent or duplicated systems, and thus may require greater interhemispheric communcation than does asymmetric functional organization. Since the nCRH had a larger callosum than CRH, it is suggested that the larger callosum may allow for greater communication required for greater bihemispheric functional representation. The hypothesis of greater interhemispheric communication in nCRH was tested in a psychological study. It was found that a group of nCRH performed better than CRH on motor and tactile tasks requiring interhemispheric transmission of information for their completion (Potter and Graves, 1988).

Axonal elimination as a factor in lateralization

The larger callosum in nCRH than CRH men could reflect various histological differences, such as greater myelination, thicker fibres, different fibre packing density, or similar density but a greater total number of fibres, particularly in those regions in which the callosum is expanded, such as the isthmus. A greater number of fibres in the posterior body of the callosum could support the postulated greater interhemispheric communication underlying the greater bihemispheric representation of language and spatial perceptual functions in left than right handers.

Although the human callosum is developed in position and shape early in fetal life, it more than triples its overall size during postnatal development (Rakic and Yakovlev, 1968). Studies of quantitative electron microscopy in the cat (Koppel and Innocenti, 1983) and in the rhesus monkey (LaMantia and Rakic, 1984) indicate that new callosal axons do not develop postnatally. Comparable studies are not available in man, however, a review of the available studies of gross size of the human callosum during development shows an approximately constant ratio of callosal size to brain size from birth to maturity (Witelson and Kigar, 1988*b*; fig. 4), compatible with a situation of no increase in callosal fibre number.

In contrast, there is extensive evidence that there is a decrease in the number of axons throughout the vertebrate brain in prenatal and early postnatal periods (Cowan *et al.*, 1984). The number of callosal axons at birth was found to be markedly higher than at maturity in the cat (Koppel and Innocenti, 1983) and in the monkey (LaMantia and Rakic, 1984), suggested to be the result of axonal elimination during the regressive events in the early stages of neural development. In the context of such neurobiological observations, it may be more fruitful to consider what may lead to fewer fibres in CRH males than what leads to more fibres in nCRH. CRH males may undergo more extensive axonal elimination of callosal fibres.

Larger brains might be expected to have larger parts. The observed correlation ($r = 0.48$) between total callosal area and cerebrum weight for the total group is consistent with this notion and suggests that some common growth factors may influence both brain and callosal size. Other studies reporting brain weight found similar correlations. In both the studies of Bean (1906) and Mall (1909), callosal size was correlated with brain weight (in Bean: $r = 0.62$ for the total group of Caucasian adults ($n = 45$, $P < 0.01$); $r = 0.69$ for the total group of 'Negro' adults ($n = 72$, $P < 0.01$); in Mall: $r = 0.76$ for the 'White' group ($n = 17$, $P < 0.01$) and $r = 0.35$ for the 'Black' group ($n = 49$, $P < 0.02$), calculated by the present author from the raw data of the original reports). In contrast, Demeter *et al.* (1988) found no significant correlation between callosal size and brain weight in a sample of 35 brains ($r = 0.26$, $P > 0.1$).

In the present study, all callosal regions showed significant correlations with brain size, except for the posterior body segments which did not correlate with cerebrum weight, specifically in CRH. This pattern suggests that in addition to general growth influences, some factor such as the postulated greater axonal elimination, may operate to determine the smaller posterior callosal body in CRH males.

There may be a point along a continuum of neural regressive events which dichotomizes males into CRH and nCRH. In a minority of men, approximately one-third, the callosum in general, but particularly the posterior body, may undergo axonal elimination only up to some point, and these may be the individuals who have larger callosa, manifest as nCRH and have less functional asymmetry. In the majority of men, axonal elimination may proceed beyond this point, and these may be the individuals who manifest with smaller callosa, CRH and greater functional asymmetry. Fewer callosal fibres could be associated with fewer cortical neurons. In a study of regional cerebral blood flow (Gur *et al.*, 1982), a lower percentage of grey matter was reported for right-handed males than for left-handed males or females in general, a pattern analogous to that of the present results. In a vein similar to the hypothesis of greater axonal elimination in CRH males, Galaburda *et al.* (1987) recently suggested that asymmetry in the planum temporale in the human brain is a result of reduction in the size of the planum on one side, due to asymmetric neuronal cell death in early development.

Sex differences in callosal morphology

Following the report of a sex difference in callosal anatomy by de Lacoste-Utamsing and Holloway (1982), several other studies examined possible sex differences in the callosum, all with negative results except for a second report by Holloway and de Lacoste (1986). In the present study, four sex differences in callosal anatomy were observed. (1) The total callosum, the genu, and the anterior midbody were greater in absolute area in males than females. These differences were proportional to overall brain size. (2) In contrast, the isthmus tended to be larger in absolute area and was significantly larger in relative size in both female groups than CRH males. (3) Handedness was not associated with callosal size in females, but it was in males. (4) Callosal area decreased with advancing chronological age in males, but not in females.

Sex differences in the genu, and not in the splenium

The results of all the studies the author could find concerning sex differences in the human callosum are summarized in the Appendix (11 reports and 3 abstracts). Total callosal area tended to be larger in males than females in 8 of the 10 studies which reported mean values. In 2 of these (Bean, 1906, 'Negro' groups; present study), the sex difference reached statistical significance. Although males are known to have larger brains, most studies did not report brain weight. Brain size (specifically cerebrum weight) was statistically controlled in 2 of the studies (Weber and Weis, 1986; present study). Even with brain size considered, no sex difference in favour of females emerged, and the results indicated that the sexes did not differ in overall callosal size relative to brain size.

Of the 14 studies, only 1 found a statistically larger total callosal area in females than males (Holloway and de Lacoste, 1986). The samples in this study appear atypical in other respects, and the method of sample selection was not given. The male group had a mean brain weight of 1248 g (with the minimum value as low as 936 g), not much larger than the mean of 1202 g for the females, who were a decade older. The mean callosal area of the female group was the largest value of any male or female group in any study. Moreover, the mean value of 744 mm^2 for the female group (*see* Appendix) is a mean of very disparate values: 712 mm^2 and 770 mm^2, obtained separately by each of the authors (Holloway and de Lacoste, 1986; Table 1).

The splenium itself has received considerable attention in the study of sex differences. Absolute area of the splenium was reported in 7 studies. In 5, males tended to have the larger value, although the difference never quite reached statistical significance (Bean, 1906; Mall, 1909; Witelson, 1985; Weber and Weis, 1986; Demeter *et al.*, 1988; present study), nor was any sex difference for the splenium reported in any of the 3 abstracts. Only 1 study (de Lacoste-Utamsing and Holloway, 1982) reported a sex difference, in the opposite direction, with females having a larger splenial area at the $P = 0.08$ level. Splenial area was not reported in their second study (Holloway and de Lacoste, 1986). A linear measure of splenial size—maximal splenial width—was found to be greater for females than males in the 2 de Lacoste and Holloway papers. However, a linear measure does not necessarily indicate a larger structure overall as does area.

Since males have larger brains and also tend to have larger callosa, splenial size was considered relative to baseline measures in a few studies. Even such analyses did not reveal larger values for females. No difference was found for splenial area relative to cerebrum weight (Weber and Weis, 1986; present study), or relative to total callosal area (present study; several studies that examined this measure, except the Clarke *et al.*, 1986 abstract which reported a difference but without data). No sex difference for splenial width, on its own, or relative to brain size was found in any study other than the de Lacoste and Holloway reports.

A few studies have examined possible sex differences in callosal size during development. No sex difference in area of the total callosum or splenium was found in children (e.g., Bell and Variend, 1985). The only sex difference observed was for splenial width during fetal life (de Lacoste *et al.*, 1986). A detailed review of the few developmental studies is given elsewhere (Witelson and Kigar, 1988*b*).

In summary, in almost all studies it was the male group which tended to have larger total callosal and splenial areas. When brain size was controlled, females still did not have larger callosal values. Reliable sex differences were not observed during development. In spite of all the recent discussion of a larger callosum in females than males, such a sex difference was found in only 2 of the 14 studies, both by de Lacoste and Holloway. Sample size was small in both studies and the sex difference was based on different anatomical measures in the 2 studies.

Another factor that may contribute to the inconsistent results is racial origin. For example, a recent study of groups of 'American Indian', 'Black' and 'White' subjects reported that the degree of right-left asymmetry in the frontal and occipital lobes varied with race (McShane *et al.*, 1984). The results of Bean (1906), although not those of Mall (1909), suggested that splenial area relative to total callosal area may be larger in 'Negroes' than 'Caucasians' (*see* Appendix). The mean ratio of splenial to total area was calculated by the author for each study where possible (Appendix). Most studies did not specify racial origin, but the source of cases could give some indication. Visual inspection of the ratios suggested that samples likely to include only Caucasian subjects had lower ratio scores than samples likely to involve both Blacks and Caucasians. The samples in the de Lacoste and Holloway studies did include both racial groups, and were small. If by chance a larger proportion of Blacks occurred in the female than male groups, this factor could contribute to the inconsistent results of these studies.

In the present study, possible sex differences in callosal regions other than the splenium were examined. Most anterior regions tended to be larger in males than females, as was the case for the splenium. For the genu and anterior midbody, the differences were statistically significant. With cerebrum weight controlled, the sex differences disappeared, indicating that the genu and anterior midbody were absolutely larger in males, but not larger in proportion to brain size. These regions were not measured in most other studies. The ratio of genu (defined to include the rostrum) to total callosal area was reported in the study by Oppenheim *et al.* (1987), and no sex difference in proportional size was observed, as in the present study.

The larger brain and larger callosum in males might be expected since males are taller and have larger bodies. Brain weight correlates significantly with height and body weight (for example, $r = 0.47$ and 0.29, respectively (Holloway, 1980)). Thus sex differences might be expected in absolute brain size to be most prominent in regions related to primary or secondary sensorimotor representation (as may be the case for the anterior midbody of the callosum) and less marked in a region such as the genu—associated with the prefrontal lobes which have more general, hierarchical functions such as attention, integration, and formulation of thought and behaviour (Stuss and Benson, 1986).

Sex difference in the isthmus

The isthmus showed sex-related differences. In males, the hand groups differed; in females, they did not. In addition, both female hand groups tended to have a larger isthmus in absolute area and did have a larger isthmus relative to total callosal area and to cerebrum weight compared to CRH males. This sex difference would involve the large majority of people (approximately 83%). Other studies did not measure this region separately. The recent report of Byne *et al.* (1988) indicated that minimal width of the body of the callosum was greater in females than males. Location of the width measure was not specified, but it is likely that it usually occurred in the isthmus, based on other reports of callosal morphology (Malobabic *et al.*, 1985).

The sex difference in the isthmus is unique in that only in this callosal segment were females found to have a larger region. The larger isthmus in female CRH than male CRH is compatible with the neuropsychological hypothesis of greater bihemispheric representation of cognitive functions in females than males (e.g., Beaton, 1985); it is compatible with the more specific hypothesis of greater bihemispheric representation of cognitive functions in females for only posterior cortical regions, with females having speech and other praxic functions more focally represented in left frontal regions (Kimura, 1987), and it is compatible with the existence of sex differences in performance on some linguistic and spatial tasks (e.g., Bradshaw and Nettleton, 1983) which may be dependent on the temporal and parietal cortical regions which send fibres through the isthmus.

Although the sexes do not appear to differ reliably in splenial size as initially suggested by de Lacoste-Utamsing and Holloway (1982), the impetus of their work may lead to the delineation of other sex differences in callosal morphology.

Sex difference in callosal anatomy in relation to laterality

The possibility of a hand × sex interaction in callosal size seen in an earlier study (Witelson, 1985) was clearly revealed with the analysis of subregions. The two posterior body regions which most differentiated CRH and nCRH did so in interaction with sex. Male hand groups differed, female groups did not. The lack of difference between the female hand groups is not likely due to insufficient power as the magnitude of the difference was small and the groups were twice as large as the male subgroups. These results suggest that anatomical variation of the callosum may be less associated with functional asymmetry in females than males, and that the factors leading to hand preference and pattern of hemisphere specialization may be different in the sexes. Axonal elimination, proposed as a factor in shaping the callosum in relation to lateralization in males, may not have such a role in females.

The sex differences in callosal morphology and its correlates raise the possibility that prenatal sex hormones have a role in the mechanisms determining callosal anatomy. Other researchers have discussed the possible role of sex hormones in determining the pattern of functional asymmetry and cognitive skills, based on studies of sex differences in perceptual asymmetry and in deficits associated with unilateral brain damage (e.g., Kimura, 1987) and the association of left handedness and autoimmune disorders (Geschwind and Behan, 1982). The effects of early levels of sex hormones on brain anatomy and behaviour in many nonhuman species are well documented (e.g., Goy and McEwen, 1980). The role of perinatal testosterone in determining callosal size has recently been shown in the rat. Female rats given testosterone in infancy developed significantly wider callosa in several regions compared to control females, and showed callosa comparable in size to normal males (Fitch *et al.*, 1987). In humans, genetic females with atypically high early levels of androgenizing hormones, for example, females with congenital adrenal hyperplasia (Nass *et al.*, 1985) or exposed prenatally to the synthetic oestrogen, diethylstilboestrol (Hines and Shipley, 1984), and males such as Klinefelter individuals (47,XXY) (Netley and Rovet, 1984) in whom perinatal levels of testosterone may be reduced (Sørensen *et al.*, 1981), have been reported to have atypical patterns of hand preference and functional asymmetry. Callosal size in such populations remains to be determined.

Sex difference in the relation of callosal size with age

The fourth main sex difference observed in the present study concerns the association between callosal size and advancing chronological age. In both CRH and nCRH male groups, high correlations were found ($r = -0.73$ and -0.86, respectively), which were statistically significant even though sample size was small. In contrast, the two female hand groups showed nonsignificant correlations of -0.11 and 0.05, with the total female group showing a correlation of -0.05. From these data, it appears that at least in the age interval of 25 to 68 yrs, callosal size decreases with age in men, but remains constant in women. Analysis of Bean's (1906) data revealed a similar sex difference in the correlation of brain weight and age for the age interval of 24 to 87 yrs [for Caucasian males, $r = -0.32$ ($n = 37$, $P = 0.05$); for Caucasian females, $r = -0.08$ ($n = 8$)]. Demeter *et al.* (1988) reported no correlation of total callosal area with age for the total group which varied from 20 to 91 yrs of age ($r = -0.02$, $n = 35$). A correlation for males may have been masked by their analysis which combined the sexes. Decrease in callosal size may reflect a sex difference in histological changes, such as the loss of synaptic connections and callosal collaterals. A different or earlier ageing process may occur in the brains of men than in women.

In conclusion, the findings of a set of associations of callosal morphology with the factors of hand preference, sex, cerebrum weight and chronological age, suggest that individual differences in the anatomy of the callosum are not random and warrant consideration of the hypothesis that anatomical variation in the callosum may have functional consequences. Variation in gross callosal anatomy may serve as a window for individual differences in cortical histology, heretofore not suspected. The nature of such possible histological differences, such as neuronal cell packing density, may shed light on mechanisms leading to neuroanatomical variation and associated psychological variation among people.

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ADDENDUM

Since this paper was completed the author has learned of another report in which the midsagittal area of the corpus callosum, assessed by MR, was found to be 11% larger in non consistent-right-handers than in consistent-right-handers (Habib M. *International Journal of Neuroscience*. In press).

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APPENDIX

SUMMARY OF STUDIES OF SEX DIFFERENCES IN THE CORPUS CALLOSUM AND THE SPLENIAL REGION IN HUMAN ADULTS

		Sample						*Splenium (posterior 1/5)*		
Study	*Method*	*Sex*	*n*	*Age (yrs)*	*Race*	*Brain weight (g)*	*Callosum (CC) Total area (mm^2)*	*Width (mm)*	*Area (mm^2)*	*Area/CC*
Bean, 1906[a]	PM[b]	Male	53	53	Caucasian	1304	691	—	173	0.25
		Female	14	51		1105*	634 n.s.	—	164 n.s.	0.26
		Male	52	45	Negro	1216	635	—	186	0.29
		Female	28	43		1068*	571*	—	173 n.s.	0.30
Mall, 1909[a]	PM	Male	50	—	Negro	1312[c]	575	—	143	0.25
		Female	20	—		1222*	548 n.s.	—	137 n.s.	0.25
de Lacoste-Utamsing and Holloway, 1982	PM	Male	9	37[d]	—	1379	704	11.4	186	0.26
		Female	5	28		1205*	708 n.s.	16.4*	218 n.s.	0.31
Witelson, 1985	PM	Male	12[e]	48	Caucasian	1471	725	—	189	0.26
		Female	30	50		1258*	670 n.s.	—	174 n.s.	0.26
Holloway and de Lacoste, 1986	PM	Male	8	64	Caucasian and Negro	1248	618	10.3	—	—
		Female	8	73		1202	744*	13.3*	—	—
Nasrallah *et al.*, 1986	MR[f]	Male	11	Total = 28	—	—	705	—	—	—
		Female	10			—	605 n.s.	—	—	—
Weber and Weis, 1986	PM	Male	18	73	—	1030[g]	640	17.2	165	0.26
		Female	18	77		890	613 n.s.	17.7 n.s.	162 n.s.	0.26
Kertesz *et al.*, 1987	MR	Male	51	Total = 30	—	—	724	—	—[h]	—
		Female	53			—	716 n.s.	—	—	—

		Sample					Callosum (CC)	*Splenium (posterior 1/5)*		
Study	*Method*	*Sex*	*n*	*Age (yrs)*	*Race*	*Brain weight (g)*	*Total area (mm²)*	*Width (mm)*	*Area (mm²)*	*Area/CC*
Oppenheim *et al.*, 1987	MR	Male	40	—	—	—	—	%CC 23.7	—	0.30
		Female	40	—		—	—	24.1 n.s.	—	0.31
Demeter *et al.*, 1988	PM	Male	22	64	—	—	627	11.8	165	0.26
		Female	12	58		—	582 n.s.	11.6 n.s.	165 n.s.	0.28
Byne *et al.*, 1988	MR	Male	15	47	—	—	519	10.7	160	0.31
		Female	22	36			601 n.s.	11.5 n.s.	170 n.s.	0.29 n.s.
Witelson, present study	PM	Male	15	50	Caucasian	1455	719	13.5	188	0.26
		Female	35	51		1250*	657*	12.7 n.s.	173 n.s.	0.26
Abstracts										
Clarke *et al.*, 1986	Some PM, some MR	Male	32	—	—	—	— Not	—	— Not	—
		Female	26	—		—	— different	—	— different	—
Harris *et al.*, 1987	MR	Male	12	—	—	—	— Not	— Not	— Not	—
		Female	12	—			— different	— different	— different	—
Yoshii *et al.*, 1987	MR	Male	14	—	—	—	— Not	—	— Not	—
		Female	19	—			— different	—	— different	—

— = no values given. * Significant difference ($P \leqslant 0.05$) between the paired values. n.s. = nonsignificant difference ($P > 0.05$) between the paired values.

[a] Independent t tests were done by SFW based on the raw data presented in the original report. Differences significant at the 0.05 level are indicated. [b] Postmortem, direct measurement. [c] Mean brain weights are based on only 36 males and 13 females. [d] de Lacoste, June, 1983; personal communication. [e] For each sex group, CRH and nCRH groups were combined as their proportions were typical of the general population and therefore similar to what might be expected in the unselected samples of the other studies; and because no sex x hand interaction was found for total callosal or splenial measures. These 42 cases were included in the present study. [f] Measures from in vivo MR scans. [g] Only cerebrum weight was given. [h] Kertesz *et al.* reported no sex difference for splenial area, but no definitions of the region or values were given.

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BOOK REVIEWS

Current Neurology, Volume 8. Edited by Stanley H. Appel. 1988. Pp. 363. London: Wolfe Medical. Price £49.00.

The eighth volume of this useful series does not attempt an overall update in neurology but consists of 10 important review articles by US contributors, many of whom are from Houston. The collection starts with an excellent article outlining the recent advances in the understanding of Duchenne muscular dystrophy in a way that will appeal to clinical neurologists, as it is easily understandable and pragmatically outlines the implications for the screening of carriers, emphasizing that although the situation has vastly improved there are still some important limitations. Helpfully for the clinician, the chapter includes discussion on the timing and urgency of referrals as well as the need for accurate diagnosis, proper pedigrees, CK measurements and adequate handling of samples during shipment. There follows a chapter on infectious peripheral neuropathies that discusses the possible mechanisms whereby an infectious agent can damage nerves directly or indirectly. More specifically there are reviews on leprosy, varicella/zoster neuritis and, topically, Lyme disease. Naturally the various neuropathies associated with HIV infection, including the Guillain-Barré syndrome, a distal symmetric and predominantly sensory neuropathy, mononeuritis multiplex and cytomegalovirus or zoster radiculoneuropathy are reviewed. Multiple sclerosis once again gets a chapter that starts by dealing with the problem of diagnosis, emphasizing that MRI scans can only be relied on in the proper clinical circumstances, as should evoked potentials and CSF findings. Blood-brain barrier defects and MS get a mention both in the context of the usefulness of gadolinium assisted MRI and in the fairly common finding of periphlebitis retinae in the acute stages of the disease. An interesting explanation for the apparent worsening of MS that occurs with intercurrent infections and when γ interferon was administered is expounded; that is that under these circumstances increased expression of surface MHC antigen on CNS glia occurs and that leads to increased inflammation. Recent therapeutic trials are discussed, as is once more the known epidemiology, genetics and HLA data, as well as the possible involvement of retroviruses.

There is a comprehensive chapter on myoclonus that includes its classification and electrophysiological evaluation. Physiological myoclonus is discussed, including the relatively recently defined neonatal sleep myoclonus. All the forms of essential, epileptic and symptomatic myoclonus are outlined. There is an interesting section on toxic causes, such as bismuth, and drug-induced causes, for instance penicillin, cephalosporins, the anaesthetic etomidate and apparently water-soluble contrast materials. A chapter on epilepsy largely discusses the opportunities and problems that the techniques of molecular biology might bring to bear on convulsive disorders. Hope is gleaned from two promising animal models of single mutations causing epilepsy: the tottering and the shiverer mice. The former apparently gets 6-7 Hz spike and wave discharges and has no observable histological abnormality but there is a large increase in noradrenergic activity.

There is an extensive and scholarly chapter on large vessel occlusive disease, analysing the effect of atheroma at various positions of the vascular tree on clinical manifestations, CT and MRI scanning, angiography and noninvasive flow studies. Some interesting clinical points are discussed such as amaurosis precipitated by bright lights—'claudication' and the alien hand of anterior cerebral artery infarcts. Alzheimer's disease, 'the disease of the century', is reviewed in a rather superficial way, at least as far as the pathological and biochemical findings are concerned. MRI gets a chapter that is strong on explanations especially as to the relative values of each of the five tissue parameters that can be measured is concerned. There is also helpful discussion, given that it is more complex than on CT, on the imaging of haemorrhage. The fundamentals of magnetic resonance spectroscopy are explained and examples of its use in muscle disease given; there are also some preliminary data on in vivo human P_{31} brain studies in stroke, tumours and dementia. Lastly, there is a chapter on the rare but interesting and treatable biotin-dependent disorders demonstrating the importance of a third, after pyridoxine and biopterin, critical cofactor in inherited neurological diseases that may later be found to be important in the acquired diseases. There is, therefore, much in this volume that will interest neurologists and it is highly recommended.

ADRIAN WILLIAMS

Essential Neurology. By I. M. S. Wilkinson. 1988. Pp. 257. Oxford: Blackwell. Price £12.95.

When an author sets out to reduce subject matter to essentials, one is inclined to look for any essential points that must surely be missing. I confess such points are few in this text. It is easy to be pedantic and one might expect, for example, binocular visual loss to be mentioned as a symptom suggestive of vertebrobasilar ischaemia; nevertheless all other details are included and omissions on the whole represent differences of personal emphasis rather than fundamental artefacts.

The author's approach is apt for students, for whom this book is designed. All too often a great deal of attention is paid in standard texts to rarities and it is refreshing to read a direct sentence, 'arteriovenous malformations occasionally occur in the head, and are capable of bleeding into the subarachnoid space, or into the substance of the brain. They are rare'. Full marks for sanity. The candour of such statements as 'The lack of specific treatment should not lead to the feeling that there is nothing one can do for patients with motor neurone disease' is common sense. The text is abundant in clear and didactic statements which can be easily assimilated by students. The use of language is careful and enjoyable to read. Statements are unambiguous, concise and yet they manage to encompass a surprising amount of basic clinical neurological information.

On first reading *Essential Neurology*, I felt that it might be too elementary for the undergraduate course. On rereading it and using it as a reference book with students on ward rounds, I changed my opinion and I now think that it is correctly aimed at the audience for which it is prepared. The opinion of final year medical students who discussed and read the text during teaching ward-rounds was that it was pitched at the correct level for medical students. It is a useful clinical primer and is a healthy stimulant to discussion.

Because of my own personal idiosyncratic reaction against excess diagrammatic representation, I was critical of the book on this score, but was taken to task by students who said they liked the diagrams as visual cues and would find them useful when 'flicking through the book during revision'. There are some excellent and valuable line drawings, but in the next edition of this book, if it is to remain true to its title, a number of elementary illustrations could be pruned or dispensed with.

Important topics and syndromes are dealt with individually and conceptually. The approach is systematic and certainly covers the territory required by the student for a broad understanding of basic principles. The important chapters are on epilepsy, headache, dementia, stroke, brain tumour, multiple sclerosis, motor neuron disease, peripheral neuropathy, muscle disease, and infections of the nervous system. This is a broad canvas; but the author has not been distracted by a desire to include too much detail, and therefore succeeds in his criteria of stating the essentials of the subject and of avoiding the dangers of over-simplification.

Essential Neurology should give students a balanced view of the elements of clinical neurology. It is an excellent book for the student to use while learning by apprenticeship to neurologists in the ward, clinic and in topic teaching, and will encourage further reading in the subject. It keeps to the basic principles and is comprehensible and uncluttered with niceties, subtleties, or ambiguities.

ANNOUNCEMENTS

American Association of Electromyography and Electrodiagnosis

The 36th Annual Scientific Meeting will be held in Washington, DC, on September 15-16, 1989. It will be preceded by AAEE Workshops on September 13 and the AAEE 12th Annual Continuing Education Courses on September 14, followed by an International Symposium on Peripheral Nerve Regeneration on September 17. Further information may be obtained from Ella M. VanLaningham, 732 Marquette Bank Building, Rochester, MN 55904, USA.

First International Congress of Movement Disorders

This will be held in Washington, DC, on April 25-27, 1990 and will be sponsored jointly by the International Medical Society for Motor Disturbances (ISMD) and the Movement Disorders Society (MDS). Further information may be obtained from the Scientific Secretary, Dr Mark Hallett, National Institute of Neurological Disorders and Stroke, Room 5N226, Building 10, National Institutes of Health, Bethesda, MD 20892, USA, or from the Secretariat, ISMD, PO Box CH-4005, Basel, Switzerland.

The Riyadh Armed Forces Hospital Second Annual International Course on Magnetic Resonance Imaging

This will be held at the Armed Forces Hospital in Riyadh, Saudi Arabia on October 2-5, 1989. Further information may be obtained from: Department of Medical Studies, Armed Forces Hospital, PO Box 7897, Riyadh 1159, Saudi Arabia (tel. (01) 4777714; telefax: 4779168).

A well-presented manual of practical clinical neurology for medical students, recommended as easy and enjoyable fundamental reading.

It is refreshing that this attempt has been made to simplify and control the over-expanded central core of knowledge demanded of medical students today. It would be helpful if other curricular subjects more tangential to medical students' needs were treated in a similar reductionist manner. This would go some way towards a necessary contraction in the heavy libraries of information that can submerge the intellect, resourcefulness and imagination of even the most capable of medical students.

J. R. HERON

Diagnostic Tests in Neurology. By G. D. Perkin. 1988. Pp. 322. London: Chapman and Hall. Price £19.95 (paperback).

Although only a little over 300 pages in length, this book represents a considerable amount of work by the author. Dr Perkin, a practising neurologist, has undertaken a comprehensive review of the literature relating to the indications for and usefulness of a wide range of clinical diagnostic tests available to neurologists. Indeed the reference lists at the end of each chapter are one of the book's strongest points, supplying the reader interested in a deeper analysis of a particular test with a host of key references.

The opening chapter gives summaries of all the major methods of investigation, and offers some criticism of their value. I found this section disappointing, lacking in helpful detail, and at times nihilistic in its conclusions. The succeeding chapters which deal with specific disorders are, however, much more extensive, analysing in detail the value and indications for diagnostic tests. These sections include the investigation of common symptoms, vascular disease, dementia, epilepsy, movement disorders, multiple sclerosis (MS), cerebral tumour, neuropathies, muscle disease and cranial nerve disorders. Three chapters are devoted to neurological emergencies.

In places the balance of the book is rather distorted; sometimes research procedures, such as detection of brain and myelin antibodies in MS, seem to overshadow more readily available techniques. Also I would have liked to have seen normal values for many of the tests quoted (e.g., normal CSF IgG/total protein ratios and normal CSF IgG/albumin index). Similarly, while the chapter on muscle disorders is comprehensive, it is almost too much so, including so many rare exceptions to the rules as to confuse the less experienced reader. Balance here is also uneven, several references being made to the diagnosis of acid maltase of deficiency, and then a statement that 'myaesthenia gravis is a rare condition . . .'. These criticisms are to a large part counteracted by a short section at the end of each subject entitled 'Recommendation' under which heading practical everyday advice is offered and is accompanied by decision making flow charts in many cases. I found myself in agreement with Dr Perkin's advice on most topics, except perhaps the recommendation that progressing stroke should be regarded as an indication for urgent angiography and carotid endarterectomy.

Overall, this book offers much practical advice and will be of help particularly to neurologists in training and general physicians seeking guidance on specific problems. Practising neurologists will also find much of interest, however, particularly as the book is an excellent source of key references for further study on a wide range of diagnostic problems.

R. E. CULL

AIDS in the Nervous System. By Richard Lechtenberg and Joanna H. Sher. 1988. Pp. 141. Edinburgh: Churchill Livingstone. Price £30.00.

The explosion of knowledge about HIV and the neurological complications in infected individuals has left all but the most energetic reader breathless. There is thus a need for review material to offer the information in a readily assimilable form. The scale of the epidemic is such that referral to subspecialists like neurologists is going to be increasingly difficult in some areas, and there is a lively debate in the American journals about the need for primary care physicians to become expert at dealing with all complications, including the frequent neurological infections. They will need to become familiar with a number of conditions hitherto considered neurological curiosities.

This book is written jointly by a neurologist and a neuropathologist for the general physician. The opening chapters on the biology of HIV and epidemiology are followed by accounts of opportunistic infections, tumours, paediatric problems, and a concluding section on treatment. It is good to see the neuropathological detail in place in each section but the clinical material is often too cryptic to provide more than a background for further reading before it can be used as a guide to practice. In particular, differential diagnosis, for example of cognitive change, is inadequately addressed. One of the most difficult problems in the care of AIDS patients is the clinical overlap in the presentations of such diverse complications as toxoplasma encephalitis, cryptococcal meningitis, lymphoma, PML, and the AIDS dementia complex. All can produce mental change, headache and focal signs. Furthermore, CT and MR scans may fail to distinguish the cause of the focal abnormalities. CSF usually shows an elevated protein and a mild pleocytosis which again is less than diagnostic. Brain biopsy or a trial of therapy may well be needed in the absence of a clear clinical diagnosis. This whole area is poorly covered though each complication is separately described in the text. One also looks in vain for help with the difficult problem of what to do if a patient with toxoplasma abscesses is allergic to sulphonamides, and what to do if somebody on gancyclovir as well as zidovudine for CMV retinitis develops leucopenia. Does one stop the gancyclovir with the risk of blindness, or stop the zidovudine losing its benefits on survival?

For those wanting more scientific background and more detailed clinical descriptions the book by Rosenblum, Levy and Bredesen is recommended, but this attractively produced volume by Lechtenberg and Sher is a useful introduction to the subject. Sadly it cannot help being out of date within two years.

M. J. G. HARRISON

Epilepsy, Behaviour and Cognitive Function. Edited by Michael R. Trimble and Edward H. Reynolds. 1988. Pp. 214. Chichester: John Wiley. Price £32.00.

This book is the result of a symposium held in the UK in 1987. The topic is highly appropriate, and relevant for clinicians both in epileptology and general neurology, as the problem of dementia is one of the main aspects that is considered. The book is well put together. The historical aspects, investigative methods and different facets of epilepsy are of particular interest, such as the influence of drug treatment.

The relationship between epilepsy and brain disorders with dementia is contrasted with the problems of epilepsy leading to dementia. The importance of seizures occurring during childhood as being a major factor in epilepsy leading to dementia is emphasized. With regard to dementia as such, it is worth mentioning its relatively low incidence in relation to epilepsy without damage or maldevelopment of the brain.

The book is a supplement which offers excellent reviews for those interested in cognitive function and in epilepsy.

AGNETE MOURITZEN DAM

Drug-induced Headache. Edited by H.-C. Diener and M. Wilkinson. *Advances in Applied Neurological Sciences*, Volume 5. Edited by R. J. Joynt and A. Weindl. 1988. Pp. 173. Berlin: Springer. Price DM 98.00.

That the injudicious use of drugs prescribed for headaches could result in headaches has apparently only recently been realized in some circles. Whether such a slender subject justifies a conference is debatable; whether it merits publication is dubious. Nonetheless, a conference took place at the University of Tübingen in 1986, and this attractive volume records the results, skilfully edited by Marcia Wilkinson and H.-C. Diener. The arbitrary six definition criteria were: more than 20 headaches per month; daily headache exceeding 10 h; intake of analgesic or migraine drugs on more than 20 days per month; regular intake of analgesics and/or ergotamine preparations in combination with barbiturates, codeine, caffeine, antihistaminics or tranquillizers; rebound headache after discontinuation of drugs; the nature of the underlying headache not being related to the syndrome.

Some distinguished contributors took part, covering clinical features, psychological, behavioural and social aspects, and pharmacology and treatment. With a tiny topic, if a not uncommon one, it is inevitable that there is far too much overlap, repetition and sometimes conflicting opinion. The publication often strays from the subject to brief reviews of platelet reactivity, an excellent overview of ergot pharmacology (Tfelt-Hansen), and an irrelevant paper on psychiatric aspects of drug addiction of the barbiturate-alcohol type (Taschner and Wiesbeck). One of the main clinical chapters (Dichgans and Diener) says more about the extracranial complications of analgesic excess than it does about headache.

What little there is to know of this common condition—a reflection of a mixture of despair, irresponsibility and poor medical supervision—is more a matter of clinical common sense than of science. Whether a conference book written by those who do know will be heeded by those who do not, is a doubtful speculation. This nicely presented volume contains the necessary facts and references.

J. M. S. PEARCE

Giant Intracranial Aneurysms: Therapeutic Approaches. By Yves Keravel and Marc Sindou *et al.* Translated by S. Rao. 1988. Pp. 163. Berlin: Springer. Price DM 248.00.

Giant aneurysms—that is, aneurysms with a diameter of over 2.5 cm—are relatively rare. The average British neurosurgeon who treats perhaps 40 to 50 patients with aneurysms per year will only see a giant aneurysm once every 18 months. Depending upon its situation, a giant aneurysm can give rise to a variety of symptoms. These aneurysms often present formidable management problems and of necessity few neurosurgeons can accumulate much experience in this field.

They thus form an entirely suitable subject for a monograph such as this. It has been written by two French neurosurgeons and was originally published in the French language in 1984. Based partly on their own experience, partly on a review of the literature, this book explores every aspect of the aetiology, pathology, investigation and treatment of these fascinating lesions. This slim volume is beautifully produced and lavishly illustrated. It provides an invaluable source for reference but has, unfortunately, one major defect which often characterizes a medical textbook which has been translated into English from another language—it is virtually impossible to read with ease. Often a passage requires rereading and then careful scrutiny before the meaning becomes clear. Whether this difficulty reflects the fact that the translation has been carried out by a person for whom the text means nothing or whether it reflects some fundamental neurophysiological difference between anglophones and others is difficult to decide, but it does point to a major obstacle to scientific communication between neurosurgeons of different mother tongues. Perhaps all books such as these should be first translated by a professional translator and then completely redrafted by a neurosurgeon who is both a native speaker of the language concerned and tolerably literate.

R. S. MAURICE-WILLIAMS

Neurodegenerative Disorders: The Role Played by Endotoxins and Xenobiotics. Edited by G. Nappi, O. Hornykiewicz, R. G. Fariello, A. Agnoli and H. Klawans. 1988. Pp. 326. New York: Raven Press. Price $86.50.

The possibility that endogenous or environmental neurotoxins contribute to the incidence of neurodegenerative diseases is a fascinating concept. Several recent discoveries have fired this area of research. In particular, impetus has been provided by the ability of MPTP to destroy *nigral* dopamine-containing cells and to induce parkinsonism, and the involvement of nonprotein amino acids in the aetiology of ALS of Guam and lathyrism. These new concepts, coupled with the ability of metals, drugs and solvents to cause damage to both the peripheral and central nervous systems, make this an area well worthy of presentation in a single volume.

This volume represents the proceedings of the International Symposium of Neurotoxicology (Turin, Italy) held in 1987. It is presented in the camera-ready form usual for such conference proceedings and which immediately detracts from the impact such books make. The 30 contributions are considered under a number of different headings, namely endo- and exotoxic causes of mental decline, neurotoxicology of Parkinson's disease, toxic abnormal involuntary movements, toxic motor neuron diseases, and peripheral neuropathies and ethanol. This, however, disguises the mixed nature of many of the sections. For example, Horowski's excellent chapter on new ergots for Parkinson's disease is considered under toxic abnormal involuntary movements. Nevertheless, the book contains many interesting and detailed articles despite its highly diverse nature.

What becomes clear throughout the volume is that different approaches to the study of the cause of such neurodegenerative illnesses are necessary if we are to understand the disease process. Only then can restorative or preventive treatments be implemented. Indeed, the volume contains a number of articles which consider the ability of acetyl-L-carnitine to protect against neurotoxic insults.

In conclusion, this is a timely if diverse volume in which many will find articles of interest.

P. Jenner

Sleep Disorders: Diagnosis and Treatment. Edited by Robert L. Williams, Ismet Karacan and Constance A. Moore. 1988. Pp. 413. New York: John Wiley. Price £38.95.

The first edition appeared 10 years earlier and the new one is extensively revised. There are chapters discussing nocturnal myoclonus and the restless legs syndrome, sleep and schizophrenia, sleep apnoea, ageing and sleep disorders, and many other topics. A Bologna team headed by Lugaresi write on sleep in clinical neurology.

There continues a bias towards the laboratory rather than the clinic. I felt it should be explained to the reader that there is no established clinical importance for, for example, the duration of REM sleep in the night: the reader might otherwise have thought that the chapter cataloguing effects on EEG sleep stages of a long list of drugs was of relevance to the care of his patients.

It is a pity that no mention is made of the evidence that triazolam is a hypnotic to avoid because, taken regularly at night, it causes anxiety by day, as Dutch, British and American investigators have found over a period of years (e.g., Bixler, Kales, Brubaker and Kales (1987) *Pharmacology*, **35**, 286–300). The discussion and the reference list on the subject of nocturnal rocking is perfunctory, with night terrors and sleepwalking doing little better. There is no mention of the extensive literature on the provocation of these latter phenomena by a wide range of CNS drugs: matters of considerable importance to the practising clinician. The reader would also gain the incomplete notion that sleep paralysis is a phenomenon of falling asleep. The first edition rightly stated that sleep paralysis is often accompanied by anxiety over the subjective difficulty of breathing but, with a new author, no mention of this now appears, although sleep paralysis continues to be a reason why patients sometimes present to chest physicians. The remark that dependence on benzodiazepines is associated 'only with excessively high doses used for extended periods' relies on a 1978 opinion that is seriously obsolete in 1988.

In short, this is a book that has weaknesses, but at the same time I would recommend it to be purchased as the best general source-book about sleep disorders that is currently available.

IAN OSWALD

Neuropsychologische Rehabilitation. *Rehabilitation und Prevention*, Bnd 19. By D. von Cramon and J. Zihl. 1988. Pp. 404. Berlin: Springer. Price DM 120.00.

It is a very strange phenomenon that many neurologists refuse to recognize the potential impact of rehabilitation procedures in patients with neuropsychological disturbances. Even the firmly established superiority of systematic speech therapy over general encouragement, spontaneous recovery or both is acknowledged by few and denied by many. Yet, in many centres, there are groups that are engaged in the development of rehabilitation techniques for disturbances of vision, of attention, of spatial perception, of learning and memory, the planning and organization of action, and the varieties of dysarthria.

The group of Detlev von Cramon in Munich plays a leading role in the development and application of methods for rehabilitation in neuropsychology. The reviewer warmly welcomes the presentation by this group of a first account of diagnostic methods as well as specific and nonspecific therapeutic measures. Specific treatment programmes are developed on the basis of knowledge in general neuropsychology and of the particular deficits in a given patient. Psychotherapeutic assistance, family counselling and social advice have to interact in order to yield success. Great efforts must be made to integrate the brain-damaged patient into his family and to prevent his closest relatives from overprotective or, alternatively, frankly hostile attitudes.

The book well serves the purpose of providing introductory information for the uninitiated reader, but someone working in the field would like to have had more discussion on advantages or disadvantages of the various therapeutic procedures and on the assessment of neuropsychological rehabilitation.

There are many excellent books on neuropsychological diagnosis and the classification of disturbances. This is the first systematic attempt to demonstrate that neuropsychology also has therapeutic aspects, and these will certainly become ever more important. I wish that the community of neurologists would be a little more open-minded towards the potential of rehabilitation in neuropsychology!

K. POECK

Recent Advances in Epilepsy—4. Edited by T. A. Pedley and B. S. Meldrum. 1988. Pp. 266. Edinburgh: Churchill Livingstone. Price £45.00.

This is the fourth volume in a very useful series, for which the editors should be justly congratulated. The previous 3 volumes have each followed a similar pattern, consisting of 13-14 lengthy review chapters covering a mixture of clinical and experimental aspects of epilepsy, with contributions mainly from the US and UK; this edition continues this successful pattern. Herein are 12 chapters; the first 3 are critiques of experimental subjects, the next 7 are clinical chapters and the last 2 are concerned with epilepsy and the law.

Meldrum's excellent first chapter on the initiation and neuroanatomical spread of seizure activity is a comprehensive review of an exciting area of experimental work. Research in this field carries the promise of new surgical approaches to human epilepsy by stereotactic interference rather than large resections. Next follows a chapter on kindling (Moshe and Ludwig) which is also an excellent review, balanced and cautious, not—as has been a tendency elsewhere—extrapolating experimental data to human clinical situations except where clearly justified. The third experimental chapter is a customary superb review by Chapman, who has contributed to a previous volume, on amino acid abnormalities in epilepsy. Each of these experimental chapters should be required reading for the nonexperimentalist who is trying to keep abreast of developments in experimental epilepsy; each is extensively referenced and each is topical and up to date.

The clinical chapters are more variable, and here one detects a hint of exhaustion in the choice of subjects, perhaps inevitable in such a series of 4 volumes in 5 years. The first, a review of the role of the electroencephalogram in the diagnosis and management of epilepsy (Rowan and French), is a well worn subject, and this particular contribution does not cover new ground. Two related chapters, on teratogenicity of antiepileptic drugs (Yerby) and the management of seizures during pregnancy (Leppik) are also subjects often written up, although both are very well done here, and both cover work not previously known to this reviewer at least. The third clinical chapter is on epilepsy and parasitosis of the central nervous system (Bittencourt, Gracia and Lorenzana) which is a good review of an area which has been the subject of a number of recent publications. Porter contributes a chapter on new antiepileptic drugs which again goes over old ground, and which inevitably is rapidly out of date as some new drugs are withdrawn and others appear. The author commends the NIH Antiepileptic Drug Development Program as a stimulus for drug development, although in this reviewer's opinion, at least, the enormous bureaucracy engendered by the FDA and the NIH programme is a hindrance rather than an assistance to drug development (hence the great number of drugs now on trial in Europe rather than the USA?). Corpus callosotomy is again in vogue for the surgical treatment of epilepsy, and this is reviewed in a chapter by Spencer. Once more, this is a subject reviewed recently by the same author in at least three other places, but again this chapter is comprehensive and instructive. The next chapter, epilepsy and depression, has similarly been previously extensively reviewed by Robertson, who here devotes 35 pages and about 250 references to her subject, and takes a hard-edged biological approach. Finally, Fenwick writes an elegant and interesting chapter on epilepsy and the law, which was the subject of a recent published symposium, from a British perspective; there is a comment from Schmidt and Wilder giving an American view. These make a fascinating comparison, more for the similarities (and apparent absurdities) of the law on both sides of the Atlantic rather than their differences.

All in all this is another excellent volume, which can be read cover to cover with advantage by any clinician interested in epilepsy. At £45 it is expensive; Volume 1 was also published in soft cover, and it would be good to see these other editions in a cheaper soft cover too.

SIMON SHORVON

Receptors and Ligands in Psychiatry. Edited by Amar K. Sen and Tyrone Lee. 1988. Pp. 578. Cambridge: Cambridge University Press. Price £75.00.

Receptors and Ligands in Neurological Disorders. Edited by Amar K. Sen and Tyrone Lee. 1988. Pp. 319. Cambridge: Cambridge University Press. Price £45.00.

The titles of these volumes do not properly reflect their contents. 'Receptors and ligands' implies a survey of techniques and methodological approaches to the study of receptors, presumably as relevant to psychiatric and neurological disorders. But there is very little of the technical handbook in these volumes. Instead we have two collections of essays, 40 in all, which cover many aspects of neurochemistry and neuropharmacology relating to synaptic transmission in diseases of the brain. There are also chapters on other topics including neuropathology and viral infection where receptors and ligands have no especial relevance. While this is no bad thing, it does make for a certain lack of continuity; with the loss of the 'receptor' theme the editors do not seem to have provided a common thread, other than the fact that all chapters relate to laboratory neuroscience. Nevertheless, there are some gems within this odd mixture.

Almost half the first volume, 10 chapters, is taken up with different aspects of schizophrenia. The first, written by Carlsson, the Grand Old Man of dopamine research, discusses the potential importance of dopamine autoreceptors in the disease. They may well be important in the effects of neuroleptic drugs since their absence on cortical dopamine terminals is proposed as the reason for the lack of tolerance to the drug-induced increase in dopamine metabolism which occurs in cortical, but not striatal, regions of the brain, this suggesting (to some workers at least) the cortex to be the site of action of antipsychotic drugs. Unfortunately, Carlsson does not discuss this but concentrates on the neuropharmacology of autoreceptor agonists and antagonists. The other chapter on dopamine in schizophrenia, by one of the editors, Tyrone Lee, reviews postmortem studies of dopamine receptors and, while providing a valuable critique of methodology and the problem of artefactual results such as those due to prior neuroleptic treatment, is partly outdated by recent PET imaging studies of dopamine receptors in vivo. What a pity not to have had a comprehensive survey of the role of dopamine in schizophrenia, since it still provides the main working hypothesis for neurochemical studies in the disease. This is even more apparent in comparison with the next chapter, which does provide a thorough review of the involvement of one transmitter. But this is of the cholinergic system; even the author admits that this is not the most widely considered hypothesis for schizophrenia! Discussions of the more frequently studied transmitters serotonin and noradrenaline are found in the subsequent chapters, drawing heavily on blood and CSF investigations, being followed by a useful review of neuroendocrine studies in schizophrenia by Cleghorn and Brown. Two chapters on peptides complete the neurochemical approaches to schizophrenia. One is from De Wied's group discussing clinical work with gamma-endorphin and CCK-derived peptides, the other by Davis and Nemeroff on neurotensin and its relationship to dopamine in the disease. The 'viral hypothesis of schizophrenia' is a very clear and readable review which puts the theory, or collection of hypotheses as the authors would suggest, in perspective. However, it does appear out of place among the strong neurochemical emphasis that makes up much of the rest of the book. The final chapter relating to schizophrenia is from Stevens discussing neuropathology and, although covering much recent work and putting it in historical perspective, like several of the other chapters it inevitably suffers from being two years out-of-date in a fast-moving field.

These essays, while often being individually valuable and well-written, together do not always provide a balanced view of the subject. The rest of the first volume covers affective disorders in 5 chapters, mainly in terms of receptors and uptake sites to the monoamine transmitters. There is some overlap, which actually makes much of the chapter on clinical studies of receptors in affective illness redundant. There are also chapters on stress and anxiety, and some miscellaneous discussions towards the end of the book.

These last 5 or 6 essays are perhaps the most useful. Two are very technical: Young and Penney provide an introduction to 'receptor mapping by autoradiographic techniques' and Davis and Niznik describe the 'application of monoclonal antibodies' to receptor research. Both are clearly written and would be valuable to the scientist considering new approaches or the student wishing to understand the methods behind these research tools. There is a useful discussion about animal models in psychiatric research, concentrating on models for depression, and a chapter on ligands used in psychiatric research, from Leysen and Janssen, who sadly restrict themselves to neuroleptics and monoamine uptake site inhibitors, and ignore the substantial contribution made by studies using ligands specific for presynaptic and postsynaptic amino acid receptors, including the benzodiazepines, and cholinergic receptors. Perhaps the most intriguing is a chapter entitled 'Is it possible that drugs have been given the wrong way for centuries?' in which Antelman proposes that the phenomenon of time-dependent sensitization, a sort of 'reverse tolerance', indicates short-term treatment or even single doses of drug to be potentially more effective than the present approach of long-term administration.

The second volume, on neurological disorders, is a similar hotch-potch of poorly-related, and stylistically very different, essays. Two on cholinergic and GABA changes in Huntington's disease (why not a single, more comprehensive, review?) are followed by a very short chapter on dopamine in movement disorders which restricts itself to a few lesion models. A review of tardive dyskinesia from Tanner and Klawans manages to avoid even mentioning the proposed role of GABAergic dysfunction; this is a severe deficit since experimental studies suggest GABA loss to be important in the mechanism of neuroleptic-induced movement disorder. Other chapters cover Tourette's syndrome, epilepsy and Alzheimer's disease, the latter in 3 contributions, 1 on aluminium and 2 on receptors which overlap substantially. Myasthenia gravis, sleep disorders and attentional deficit disorder of childhood (surely this is psychiatry?) are also discussed. There is a useful, if somewhat superficial, introduction to receptor localization in neuropsychiatry, and a final chapter from Dunnett and Björklund on brain tissue transplantation.

I do not feel that these books have anything particular to offer that cannot be obtained elsewhere. There are several good volumes on biological psychiatry covering schizophrenia and/or depression which provide broader, more balanced and comprehensive reviews of the present state of research, and the same is true for the neurological disorders. There are also sources discussing the techniques and methods of receptor research in greater depth. While I shall find several of the chapters of use, the delay between their preparation and publication has meant that many are two or three years out of date. Few research groups, departments or even medical school libraries could justify spending £120.00 on these two volumes, when much of this information can be obtained far more cheaply elsewhere.

GAVIN P. REYNOLDS

The Neuronal Microenvironment. *Neuromethods*, Volume 9. Edited by A. A. Boulton, G. B. Baker and W. Walz. 1988. Pp. 732. Clifton, NJ: Humana Press; Bognor Regis: John Wiley. Price $94.50 US, £82.35 elsewhere.

This is an interesting series intended as a single source for the increasingly diverse range of techniques used in the neurosciences. In particular it aims to make accessible the kinds of practical detail which, while essential to implementing such techniques, usually are omitted from the primary literature. The programme editors (Boulton and Baker) are clearly pursuing this goal energetically, publishing 10 substantial volumes over the last 3 years. The series concentrates overwhelmingly on neurochemistry, which makes the series title *Neuromethods*, and its target audience of 'everyone involved in the neurosciences, both basic and clinical' rather more ambitious than the published volumes really warrant (at least that is how it seems to me as a neurophysiologist). Of the other volumes in the series, only No. 1 appears to make an effective attempt to address a wider range of the neuroscience disciplines. The remainder provide valuable, if primarily neurochemical, guides to methods on subjects such as *Amines and Their Metabolites*, *Amino Acids*, *Receptor Binding*, *Lipids and Related Compounds*, and the *Analysis of Psychiatric Drugs*.

The present volume, *The Neuronal Microenvironment*, has a markedly different approach to the rest of the series. It concerns a concept rather than a class of chemical, and certainly has a more reasonable balance of the various neuroscience disciplines. The 14 chapters cover a wide range of topics: from the physiology of the blood-brain barrier and of CSF formation; through EM, biochemical and biophysical studies of fluid compartments in the brain; to biophysical, physiological and biochemical studies of ions and ion fluxes both in vivo and in vitro. There are several interesting accounts of the technology of both cell cultures and brain slices; those on the latter particularly emphasize tissue viability, an issue which is overlooked far too often. In one or two cases the material included in this book seems to lack clear cohesion. For instance, there is a long chapter by Farley on patch clamp recording, which is certainly a readable and very practical introduction to this extremely important technique, but which fails to make explicit how this relates to the neuronal microenvironment.

All the chapters have been specially commissioned from authors who, on the whole, have taken their tasks seriously. Their approaches do vary in style and balance. All include some kind of review of the scientific issues involved, though the extent and detail vary greatly. For their 'methods', some have chosen to give a detailed, practical account of limited range of laboratory techniques centred on their own. Others have used more wide-ranging reviews of methods which would require following up in their extensive bibliographies before they could be implemented. Both these extremes, and the gradations in between, have their uses, though I personally preferred the more selective, in-depth approach. Perhaps the variation in style contributes to the book's readability (which was a pleasant surprise to me, considering the subject matter). Amongst the chapters I particularly liked were those on the measurement of ion concentrations in and around neurons, notably by Nicholson and Rice, Kimelberg and Walz, MacVicar and O'Beirne, and Pumain. These gave clear accounts of what their techniques were supposed to achieve, together with clear, up-to-date descriptions of the relevant methods with various pros and cons. However, I was less happy with some of the other chapters (a minority), which were rather less critical and less up-to-date.

There is a wealth of information on experimental methods in this book. Finding one's way around this would be helped by a better index. While the existing one is quite comprehensive, it is rather poor in distinguishing major from incidental references, and in subdividing some of the more common terms under subheadings. A little more editing would have improved matters, presumably at the expense of slowing down the rather remarkable rate of publication of this series. This book has been produced attractively enough, with few obvious typographic errors. Unfortunately, the micrographs and other photographs suffer from not being reproduced on glossy paper (presumably on the grounds of economy). I would also have preferred calibration bars actually on the micrographs to scale factors (to 4 significant figures!) in the legend.

Overall, I remain unsure as to how useful it is to collect together such a disparate range of methods applied to a concept with as many facets as the neuronal microenvironment. I certainly found several topics of direct interest to me, but I find it hard to imagine the investigator who would actually want to apply more than a small fraction of the techniques described in this rather expensive volume. However, with one or two reservations, I believe that this book, and indeed the whole series, does have a place in libraries serving neuroscientists.

JOHN G. R. JEFFERYS

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